

CATALOGUE Ver. 13

DDS

Drug Delivery Systems



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From the Biosphere to Outer Space バイオから宇宙まで

The NOF Group, pursues multi-faceted business development in nine divisions of activities based on its own technologies, NOF endeavors to realize its management philosophy of “creating new values in a broad spectrum from biosphere to outer space” by focusing particularly on the fields of “life science”, “electronics and information” and “environment and energy”

日油グループは、独自の固有技術をもとに 9 つの事業部門による多面的な事業展開をはかり、「ライフサイエンス分野」「電子・情報分野」「環境・エネルギー分野」へ注力し、「バイオから宇宙まで幅広い分野で新しい価値を創造し、人と社会に貢献する」という経営理念の実現を目指してまいります。

● Corporate Overview

Head Office : Tokyo, Japan

Founded : July 1, 1937

Capital : 204 million US\$ (as of Mar.31,2011)

Employees : 3,817 (as of Mar.31,2011)

Sales : 1.8 billion US\$ (Fiscal year 2010)
US\$=¥86.81

本 社 : 東京都渋谷区

設 立 : 昭和 24 年 7 月 1 日

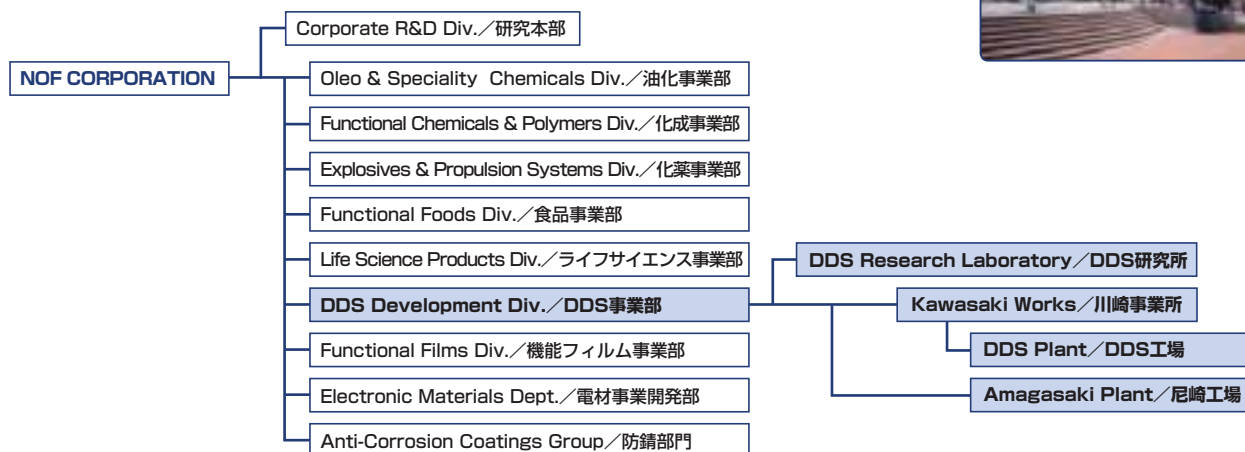
資本金 : 17,742 百万円 (2010 年 3 月 31 日)

従業員 : 3,817 名 (2011 年 3 月 31 日)

売上高 : 154,121 百万円 (2010 年度)



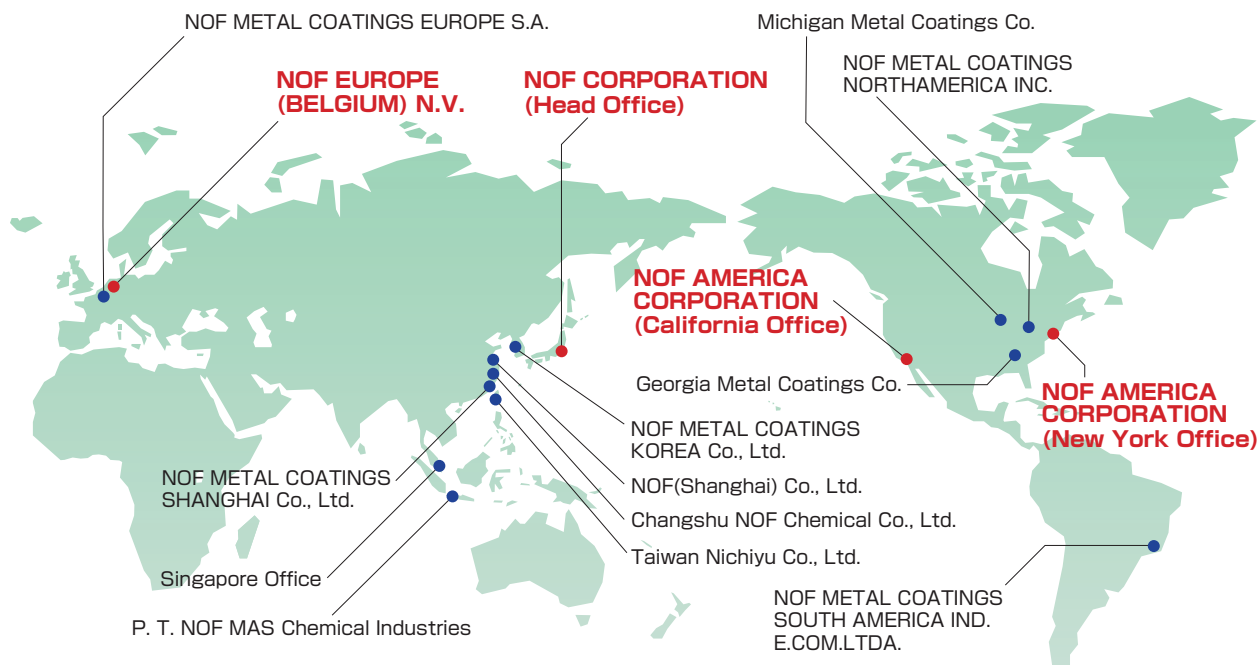
● Corporate Organization



DDS Development Division is organized within NOF's family of complementary business units, offering innovation and cGMP capabilities to pharmaceutical and biomedical products.

DDS 事業部は、日油株式会社の事業部門のひとつとして、革新的技術と cGMP 体制によって、製剤材料および製剤技術をご提供しています。

● Overseas Subsidiaries and Joint Ventures



DDS PRODUCT OVERVIEW

I . Activated PEG for PEGylation

We manufacture high-purity methoxy-polyethylene glycols (mPEGs) with molecular weights from 2kDa to 80kDa, producing high-purity activated PEG derivatives of methoxy PEG amines, maleimides and carboxylic acids. Various alterations of the terminal PEG chemistry permit drug modification as per customers' expectations and needs. Furthermore, use of PEGylated phospholipids composed of our high-purity phospholipids and PEGs prolong the plasma circulating half-life of liposome drugs.

分子量 2,000 から 80,000 までの極めて高純度のメトキシポリエチレングリコールを製造できるだけでなく、これらの原料を用いたメトキシ PEG アミン、マレイミド、カルボン酸などの活性化 PEG 誘導体も高純度、高品質で製造しています。PEG の末端基を変化させることにより、お客様の医薬品を様々に修飾することができます。また、当社の高純度リン脂質と高純度 PEG を融合させた PEG 化リン脂質を用いますと、リボソームの血中半減期を延長することができます。

II . Phospholipids and Lipids for Liposomal Formulations

In early 1990's, we commenced supply of GMP-grade phospholipids to every corner of the world. Our products have been used in commercialized liposomal drugs for anti-fungal and oncology use, which led to our outstanding reputation in this field. For the benefit of our customers, we have also developed a ready-to-use liposomal formulation, called EMPTY LIPOSOMES, into which customers can encapsulate their own drugs.

1990 年代初期から GMP グレードのリン脂質を世界に向けて供給し、市販のリボソーム医薬品に用いられ高い評価を得ています。また、顧客サイドで、その医薬品を容易にリボソーム化できる中空リボソームを開発しました。リボナイザー[®]を使用すればバッチ毎のバラツキの無いリボソームが作製出来ます。

III . Ultra-purity Polysorbate 80

Our Polysorbate 80(HX2) is the ultra-purity polysorbate 80 surfactant, and we are proud of its rating of the highest quality around the world, with less impurities compared to conventional grade. Favorable features, such as less impurities and lower susceptibility to oxidation, are responsible for negligible production of peroxides and aldehydes, which are well known to induce degradation of drug formulations. In addition, owing to its high quality, Polysorbate 80(HX2) shows superior safety features, including a lower incidence of allergic, hemolytic, cytotoxic and acute toxicity reactions compared to conventional grade.

Polysorbate 80(HX2) can be applied to various drugs as a multi-purpose surfactant, e.g., as a solubilizing agent for poorly hydrophilic drugs, as a stabilizing agent for injectable preparations containing proteins, as a stabilizer for vaccines.

Polysorbate 80(HX2) is vegetable-derived material and meets the ICH Harmonized Tripartite Guideline on New Drug Substances and Products (published, April 2006). This has validated its extensive use around the world as a standard product in the pharmaceutical field.

ポリソルベート 80(HX2) は、不純物が非常に少ない世界最高品質の親水性の高い (HLB の高い) 高純度界面活性剤です。不純物が少ないこと、酸化劣化しにくいことから、医薬品自身を劣化させる過酸化物質、アルデヒドの生成は非常に低レベルです。更に、これらの高品質を達成した結果、低アレルギー性、低溶血性、低細胞毒性、低急性毒性など、一般品にくらべて、生物学的に非常に優れた安全性を示します。

難水溶性薬物の可溶化剤、ワクチン用界面活性剤、蛋白製剤の安定化剤などの注射製剤用途をはじめ、高純度界面活性剤として、種々の医薬品用途でご使用いただけます。

非動物性原料であることに加え、2006 年 4 月より日米欧 3 局適合となり、世界標準品として幅広くご使用いただけます。

IV . Novel Excipients for Pharmaceutical Development

PUREBRIGHT[®] MB series

MPC[™] Polymers for Hydrophobic Drug Formulations

Through introduction of a hydrophilic phosphorylcholine moiety into a hydrophobic methacrylic acid polymer, we offer innovative formulation excipients for any hydrophobic drugs. Using our PUREBRIGHT MB series, any drug can be dissolved in aqueous solutions.

親水性のホスホリルコリン基を疎水系のメタクリル酸ポリマーに導入することにより、水溶性の MPC ポリマーを開発しました。このポリマーを使用して、難水溶性薬物を可溶化することができます。

Self-emulsifying Solubilizer SL-11 Novel Nano Formulation for Hydrophobic Drugs

Solubilizer SL-11 is clear liquid with superior solvent properties for many kinds of hydrophobic drugs to prepare nano emulsions with particle sizes below 50 nm. Solubilizer SL-11 is highly suitable as a SEDDS (Self Emulsifying Drug Delivery System) agent. Solubilizer SL-11 can also help increase intestinal absorption. Nano emulsions and SEDDS agents containing hydrophobic drugs can be easily prepared following simple protocols.

Solubilizer SL-11 は透明な液体で、様々な難水溶性薬剤をナノエマルジョン化することができます（粒径 50nm 以下）。また、優れた自己乳化性を有していますので、SEDDS (Self Emulsifying Drug Delivery System) 用基材として最適です。経口投与時に腸管吸収性を増大する効果も認められています。添付のプロトコールに従って難水溶性薬剤を SL-11 に溶解していただくだけで、簡単にナノエマルジョンや SEDDS 製剤をご調製いただけます。

PUREBRIGHT® SL Series Hydrophobic Drug Solubilization Kit

We supply new solubilization kits for hydrophobic drugs by using our proprietary DDS technologies. Because of the simple procedures for kit use, screening of new chemical entities and safety studies can be easily performed.

種々の DDS 技術を結集し、難水溶性薬物の可溶化キットを開発しました。キットの使用方法は極めて簡単で、安全性試験、新規開発薬剤の初期テストのスクリーニングを容易に行うことができます。

NOFABLE™ Series Ultra-Purity Oleic Acid and Derivatives

Using high-purity oleic acid, we produce the non-ionic surfactant (NOFABLE™ series) and its derivatives. Since impurities derived from oxidation are eliminated in our process for the product, any degradation and degeneration of drug formulations using it can be prevented. In addition, oil adjuvant formulation for vaccines also exploits the NOFABLE™ series.

独自の高純度に精製したオレイン酸を用いて、誘導体の非イオン界面活性剤 (NOFABLE™ シリーズ) を開発しました。酸化由来する不純物を除去していますので、医薬品の分解や変性などが防げます。さらに、NOFABLE™ シリーズを用いてワクチン用のオイルアジュバントも開発しています。

SUNBRIGHT® DKH-02HB, DKH-03HB and DKH-04HB MACROGOL (PEG-200, 300 and 400)

We have been providing ultra-pure polyethylene glycol (PEG 200, 300 and 400) as an excipient specifically useful for pharmaceutical formulations without any impurities such as EG (ethylene glycol) and DEG (diethylene glycol). We supply PEG200, 300 and 400 that meet the requirements stipulated in the USP, EP and JP /JPE.

当社は、EG (エチレングリコール) および DEG (ジエチレングリコール) の極めて少ない医薬品添加剤用ポリエチレングリコールを開発しました。

また、USP、EP、JP または JPE に適合した PEG200, 300, 400 を供給できます。

SUNBRIGHT® OE Series Biocompatible PEG Anchors for Cell Membrane Insertion [BAM]

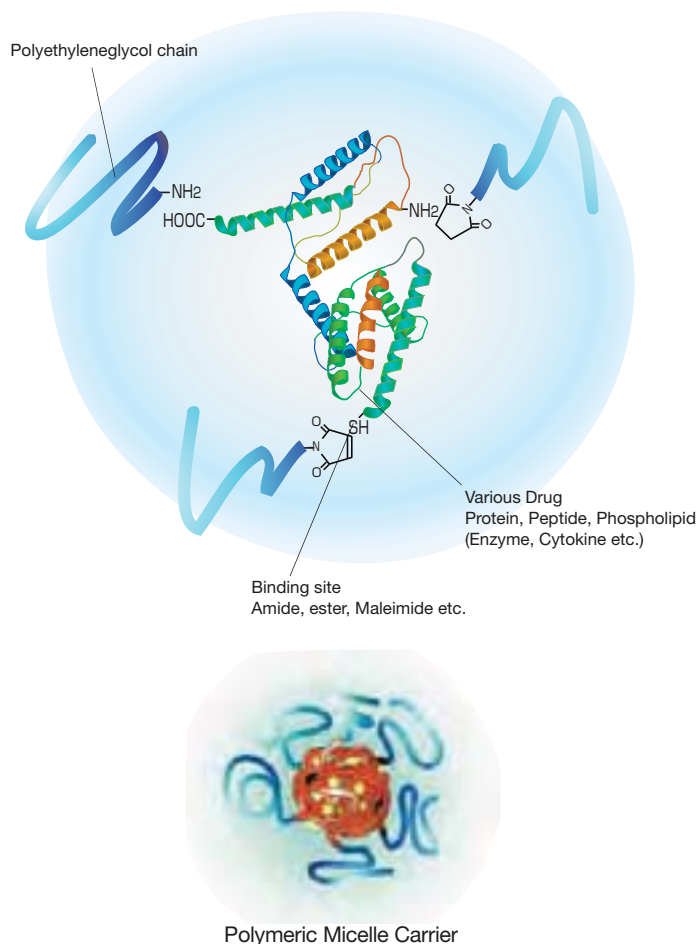
We provide a cell-modifying agent that acts without exerting any injurious effects on the cells. Employment of the BAM concept contributes to both modification of the cells or tissue surfaces with physiologically active substances, such as proteins or drugs, and live cell immobilization of cells or tissues on the surfaces of various kinds of materials without any damage to the target cells and tissues.

細胞にダメージを与えない細胞修飾剤を開発しました。BAM を用いることにより細胞や組織にダメージを与えることなく細胞や組織の表面を蛋白質や薬剤などの生理活性物質で修飾することや細胞や組織を生きたまま各種材料表面に固定化することができます。

Using these high-quality products, NOF CORPORATION provides custom formulation expertise and assistance on request.

I

Activated PEG for PEGylation <SUNBRIGHT® Series>



NOF has a long reputation for producing a high-quality Activated PEGs -the SUNBRIGHT Series- that possess the most suitable quality for preparation of physiologically active drugs and biologics. Our SUNBRIGHT series is characterized as extremely high-purity PEGs with a variety of functional groups. The products of this series are internationally recognized as optimal PEGylation drugs.

As illustrated in this figure, application of Activated PEGs with various functional groups enables introduction of PEG chains into drugs, enzymes, phospholipids and other biologics. Covalent conjugation of hydrophobic macromolecules with Activated PEGs leads to the formation of macromolecular micelles (Polymer Micelles), which allow homogeneous dispersion of hydrophobic drugs in aqueous media. Furthermore, when PEGylated phospholipids are used as liposomes, the aqueous corona added stabilizes homogeneous dispersal of the liposome preparations encapsulating drugs within them.

PEGylation plays an important role in the stabilization of drugs increased circulation time, reduction of their antigenicity and decrease in drug dosing, besides augmenting the targeting ability via binding biologics onto their surfaces.

医薬品および蛋白質などの生理活性物質の調製に最適な高品質のポリエチレングリコール (PEG) 修飾剤 - SUNBRIGHT Series - を開発しました。SUNBRIGHT シリーズは、極めて高純度で多様な官能基をもつ PEG であり、薬剤の PEG 修飾に最も適した DDS 基剤です。

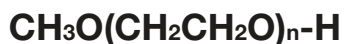
上の図に示しますように、末端に種々の官能基をもつ PEG 修飾剤を用いることにより、薬剤、酵素、リン脂質、その他生体物質に PEG 鎖を導入することが可能です。また疎水性の高分子等と PEG 修飾剤を結合させることにより、高分子ミセル体を形成し、疎水性薬剤等を水溶液中に安定に分散させることができます。以上のように、PEG 修飾をすることにより、薬剤等の安定化、抗原性の低下、投与量の低減等を図ることができ、さらに抗体等を表面に結合させることによりターゲティング性を高めることができます。

NOF's Product Advantages

High-purity mPEG-OH, Starting Material for Activated PEGs

NOF manufactures high-purity methoxy-PEG-OH characterized by absence of contaminating by impurities and narrow molecular weights distribution. These highly pure methoxy-PEG-OH have so far been used for various commercial PEGylation drugs, such as PEG-Interferon and PEG-GCSF.

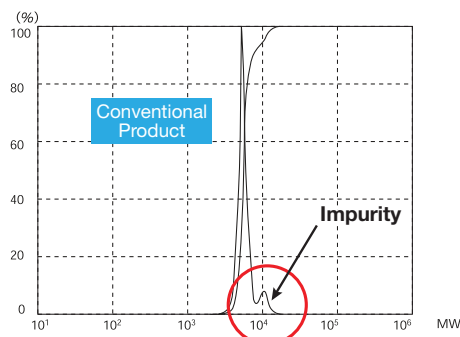
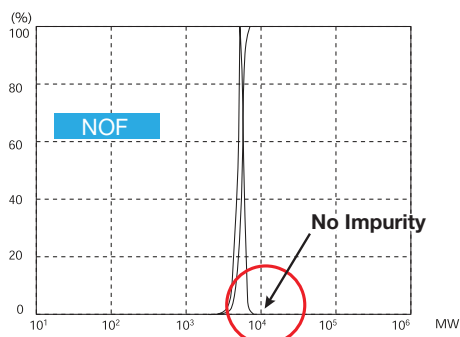
不純物がなくかつ分子量分布もシャープな高純度メトキシ PEG を製造しています。これらの高純度メトキシ PEG は、これまでに PEG- インターフェロン PEG-GCSF などの種々の PEG 修飾医薬品に使われています。



NOF CORPORATION is the sole worldwide patent holder of these high-purity mPEG-OH and all their derivatives.
※ Patent No. : JP3050228, U.S. Patent 6455639, KR 0358276

Our methoxy-PEG-OH have the advantage of extremely low diol contents relative to those of competitors' products. As shown in the following graphs, our methoxy-PEG-5000 contains remarkably low levels of diol as impurities, besides providing a narrower distribution of molecular weights in comparison with our competitors' products. Employment of our methoxy-PEG-OH as the starting materials yields higher purity and higher activity of Activated PEGs. We manufacture highly pure methoxy-PEGs with molecular weights from 2kDa to 80kDa.

当社のメトキシ PEG は、他社品に比べてジオール含量が極めて少ないことが特徴です。下図に示しますように、当社のメトキシ PEG-5000 は、他社品に比べて不純物であるジオール含量が極めて少なく、分子量分布がシャープです。当社の PEG 誘導体は、このメトキシ PEG を原料 PEG として用いていますので、修飾剤として高純度で高活性を示します。当社は、分子量 2,000 から 80,000 までの高純度メトキシ PEG を製造しています。



Comparisons of GPC analysis of NOF mPEG-OH (MW5,000) (left) and conventional product (right).

About PEGylation

PEGylation technology is applied for biologics modifications including cytokines, therapeutic antibody fragments, interleukins, hormones, oligonucleotides and other proteins and peptides.

PEGylation can be effective for :

- Improving Bioavailability
- Prolonging Blood Circulation
- Maximizing Pharmacokinetics
- Low-profile Immunogenicity

NOF provides high-performance activated PEGs for PEGylated drugs from early development stage to commercial use with our 20 years of experience of manufacturing high-quality methoxy polyethylene glycol. Our starting material for activated PEGs for pharmaceutical area. Our activated PEGs have a narrow polydispersity and low diol content with wide range of molecular weights, from 2kDa to 80kDa.

PEGylation Service

Please feel free to contact us if you need PEGylated drugs using NOF Activated PEGs, SUNBRIGHT® series. Contact : ddsinfo@nof.co.jp

PEGylation 技術はサイトカイン、抗体フラグメント、インターロイキン、ホルモン、オリゴヌクレオチド、蛋白質、そしてペプチドなどを生物学的に製剤修飾するために適用されます。

PEGylation の効果

- バイオアベイラビリティの改善
- 血中滞留時間の延長
- 薬物動態の最大化
- 抗原性の低下

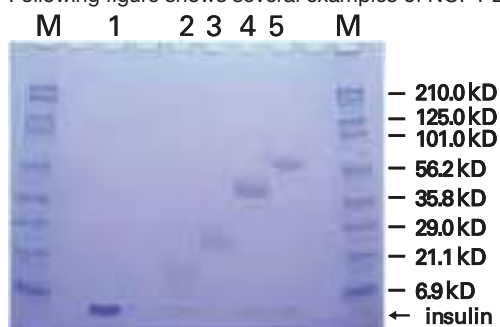
NOF は、活性化 PEG 誘導体の主原料である高純度メトキシ PEG を製造しています。この経験を生かし、PEG 修飾医薬品に用いられる活性化 PEG 誘導体を、研究初期段階の少量から商業生産スケールまでご提供いたします。当社の活性化 PEG 誘導体は、分子量分布がシャープで、かつ不純物であるジオール含量が極めて少ない高品質な製品です。分子量は 2,000 から 80,000 まで取り揃えております。

当社の活性化 PEG 誘導体を用いた PEG 修飾医薬品製造についてお気軽にお問合せください。

Reference

1) PEG-conjugation

Following figure shows several examples of NOF PEG-aldehyde conjugation with human insulin for various PEG molecular weights.



Analysis of PEG-ALD-Insulin by SDS-PAGE with Coomassie brilliant blue. Insulin was reacted with NOF PEG-ALD at 4°C. The PEGylated insulin was purified on Q Sepharose Fast Flowcolumn.

lane M molecular weight markers
lane 1 insulin
lane 2 PEG(ME-050AL)-insulin eluate
lane 3 PEG(ME-100AL)-insulin eluate
lane 4 PEG(ME-200AL)-insulin eluate
lane 5 PEG(ME-300AL)-insulin eluate

2) Coupling of PEG derivatives to Proteins: examples of simple conjugation conditions

さまざまな官能基を持つ PEG 誘導体を用いた蛋白修飾の代表例を以下に示します。

1. Coupling of PEG-NHS derivatives to protein amines (PEG-NHS + Protein-NH₂)
Conditions 1: 50 mM phosphate buffer (pH 7.2), 4°C, 6 hrs^{*1)}
Conditions 2: Borate-phosphate buffer (pH 8.0), 25°C, 2 hrs^{*2)}
2. Coupling of PEG-Aldehyde derivatives to protein amines (PEG-Ald + Protein-NH₂)
Conditions : sodium cyanoborohydride (10 equiv.), 4°C, 20 hrs^{*3)}
3. Coupling of PEG-Maleimide derivatives to protein sulfhydryls (PEG-Maleimide + Protein-SH)
Conditions: 100 mM phosphate buffer (pH 6.5), 4°C, 4 hrs
4. Coupling of PEG-NH₂ derivatives to protein carboxylates (PEG-NH₂ + Protein-COOH)
Conditions: 50mM phosphate buffer (pH 7.2), WSC (2 equiv.), 4°C, 10 hrs
5. Coupling of PEG-p-Nitrophenyloxycarbonyl derivatives to protein amines (PEG-NP + Protein-NH₂)
Conditions: borate-phosphate buffer (pH 8.0-8.3), r.t, overnight^{*2)}

References: *1) Abuchowski A. et al., *Cancer Biochem. Biophys.* **7**,175(1984)
*2) Sartore L. et al., *Appl.Biochem. Biotechnol.* **27**,45(1991)
*3) U.S.Patent 5,824,784

Capabilities

cGMP Manufacturing Facilities

NOF Activated PEGs, SUNBRIGHT® series are produced in facilities, using state-of-the-art technology, operated under cGMP. The cGMP facilities are capable of producing small to large batch sizes, using proprietary know-how with scale-up procedures, depending on customers' needs.

These cGMP facilities have been audited by pharmaceutical companies throughout the world. NOF receives a consistent high reputation from our customers.

当社は、最先端技術を駆使した cGMP 体制で、医薬用活性化 PEG ; SUNBRIGHT シリーズを生産しています。お客様のお求めに応じて、種々な製品を独自のノウハウ・技術によって様々なスケールで工業生産しています。cGMP 工場は、世界各地の製薬会社・バイオテック会社様により品質監査を受け、高い評価をいただいています。

Research & Development

Our new R&D facility was opened in December 2005. This allows us to continue our development of novel activated PEGs and new technologies for PEGylation.

2005 年に新しい研究所が川崎市に完成しました。今後も益々、医薬用の新規活性化 PEG ならびに PEGylation 技術の開発に邁進していきます。

Analytical Technologies

NOF has more than 20 years history for manufacturing of high-quality mPEGs and Activated PEGs. These experiences endow NOF with a thorough knowledge of PEGs and considerable achievement in analysis of Activated PEGs. We also invented innovative analytical methods for assaying purity of activated PEGs and for determining impurity levels.

当社は 20 年余の間、医薬用途に高純度 mPEG ならびに活性化 PEG を生産してきました。ここで得られた豊富な知識と経験から、活性化 PEG の純度分析ならびに不純物分析においても、独創的で優れた技術を有しています。



High-purity Activated PEG

Application Chart for PEG Derivatives

We supply different series of PEG derivatives with various versatile functional groups.

当社は種々の官能基を持つ PEG 誘導体を取り揃えております。

| Abbreviation | PEG Reactive group (X)* | Target groups |
|------------------------------------|---|-----------------------------|
| NHS PEG | | |
| CS | -CO-CH ₂ CH ₂ -COO-NHS | -NH ₂ , -OH, -SH |
| GS | -CO-CH ₂ CH ₂ CH ₂ -COO-NHS | -NH ₂ , -OH, -SH |
| GS2 | -CH ₂ CH ₂ CH ₂ -NHCO-CH ₂ CH ₂ CH ₂ -COO-NHS | -NH ₂ , -OH, -SH |
| GS3 | -CH ₂ CH ₂ -NHCO-CH ₂ CH ₂ CH ₂ -COO-NHS | -NH ₂ , -OH, -SH |
| AS | -CH ₂ -COO-NHS | -NH ₂ , -OH, -SH |
| HS | -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -COO-NHS | -NH ₂ , -OH, -SH |
| TS | -COO-NHS | -NH ₂ , -OH, -SH |
| p-Nitrophenyl carbonate PEG | | |
| NP | -COO-phenyl-NO ₂ | -NH ₂ |
| Aldehyde PEG | | |
| AL, AL2 | -CH ₂ CH ₂ -CHO | -NH ₂ |
| AL3 | -CONH-CH ₂ CH ₂ -CHO | -NH ₂ |
| Amine PEG | | |
| PA | -CH ₂ CH ₂ CH ₂ -NH ₂ | -COOH |
| EA | -CH ₂ CH ₂ -NH ₂ | -COOH |
| Tiol PEG | | |
| SH | -CH ₂ CH ₂ -SH | -SH, -Maleimide, -COOH |
| Maleimide PEG | | |
| MA | -CH ₂ CH ₂ CH ₂ -NHCO-CH ₂ CH ₂ -Maleimide | -SH |
| MA2 | -CH ₂ CH ₂ -NHCO-CH ₂ CH ₂ -Maleimide | -SH |
| MA3 | -CH ₂ CH ₂ CH ₂ -NHCO-CH ₂ CH ₂ CH ₂ CH ₂ -Maleimide | -SH |
| Iodoacetamide PEG | | |
| IA | -CH ₂ CH ₂ CH ₂ -NHCO-CH ₂ I | -SH |
| Aminoxy PEG | | |
| CA | -CONH-CH ₂ CH ₂ -ONH ₂ | -CHO |
| Hydrazide PEG | | |
| HZ | -(CH ₂) ₅ -CONH-NH ₂ | -CHO |

* PEG Reactive group (X)
-O-(CH₂CH₂O)_n-X or -O-X

Custom Manufacturing

NOF has over 20 years of experience in supplying high-quality methoxy polyethylene glycol (mPEG) to pharmaceutical markets. The highest quality mPEG is our starting material of PEG derivatives, patented through our proprietary technology.

Based on our extensive range of technological know-how and capabilities, NOF offers custom manufacturing from early stage development to commercial scale.

20 年余の医薬用高純度 mPEG ならびに活性化 PEG のビジネス経験を生かし、お客様のカスタム合成のご依頼に対応することができます。

高度技術および独自ノウハウを用い、早期研究段階から商業生産段階にいたるまで、様々なステージで受託生産の検討が可能です。

1. Monofunctional Linear PEGs

The mono-functional SUNBRIGHT® series comprising highly purified methoxy PEG as the starting material contains negligible bifunctional PEG derived from diol impurities. Accordingly, bridging reactions (sidereaction), an obstacle to PEGylation can be completely prevented.

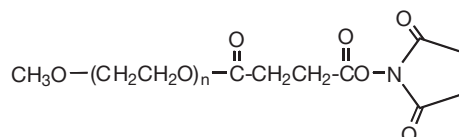
SUNBRIGHT® シリーズの一官能活性化タイプは、高純度のメトキシPEGを原料として用いていますので不純物であるジオール由来の2官能PEGをほとんど含んでいません。そのためPEG修飾時に問題となる薬物の架橋反応を防止できます。

•SUNBRIGHT® CS, GS, AS, HS and TS Series (NHS active esters/carbonate)

We supply five types of monomethoxy-NHS activated ester/carbonate-PEGs that differ in terms of the NHS carboxylate attachment chemistry. The reactivity order of these linkers in aqueous solution from lowest to highest is HS<TS<GS<CS<AS. After PEGylation, CS and GS types possessing ester groups are relatively susceptible to hydrolysis, whereas AS, TS and HS types are resistant to hydrolysis because of their different chemical structures. Therefore, our customers can select the appropriate type according to the purposes among the five types available.

カルボキシル基の結合形式が異なる5タイプのNHS活性化エステル-PEGをそろえています。水溶液中での活性化エステルの反応性は、HS<TS<GS<CS<ASの順に高く、それに伴い、中性水溶液中での安定性は、AS<CS<GS<TS<HSの順になります。また、PEGylation後にエステル結合を有するCS、GSタイプによる conjugate 体は、比較的加水分解されやすく、AS、TS、HSタイプの場合は加水分解されにくい構造となっています。従って、目的に応じて5タイプの中から適切なものをお選び頂けます。

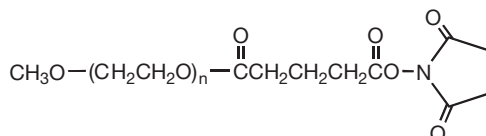
CS Type



| Product name | MW |
|---------------------|--------|
| SUNBRIGHT ME-020CS | 2,000 |
| SUNBRIGHT ME-050CS | 5,000 |
| SUNBRIGHT ME-100CS* | 10,000 |
| SUNBRIGHT ME-200CS* | 20,000 |
| SUNBRIGHT ME-300CS* | 30,000 |
| SUNBRIGHT ME-400CS* | 40,000 |

* : make-to-order

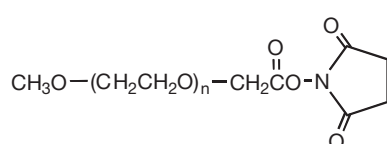
GS Type



| Product name | MW |
|--------------------|--------|
| SUNBRIGHT ME-050GS | 5,000 |
| SUNBRIGHT ME-100GS | 10,000 |
| SUNBRIGHT ME-200GS | 20,000 |
| SUNBRIGHT ME-300GS | 30,000 |
| SUNBRIGHT ME-400GS | 40,000 |

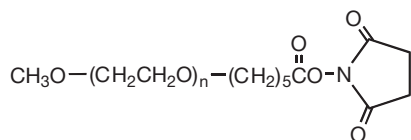
New

AS Type



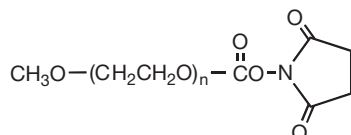
| Product name | MW |
|--------------------|-------|
| SUNBRIGHT ME-020AS | 2,000 |
| SUNBRIGHT ME-050AS | 5,000 |

HS Type



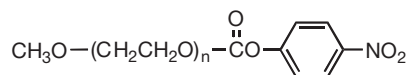
| Product name | MW | |
|--------------------|--------|-----|
| SUNBRIGHT ME-050HS | 5,000 | |
| SUNBRIGHT ME-100HS | 10,000 | New |
| SUNBRIGHT ME-200HS | 20,000 | |
| SUNBRIGHT ME-300HS | 30,000 | |
| SUNBRIGHT ME-400HS | 40,000 | |

TS Type



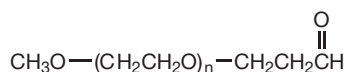
| Product name | MW | |
|--------------------|--------|--|
| SUNBRIGHT ME-050TS | 5,000 | |
| SUNBRIGHT ME-100TS | 10,000 | |
| SUNBRIGHT ME-120TS | 12,000 | |
| SUNBRIGHT ME-200TS | 20,000 | |
| SUNBRIGHT ME-300TS | 30,000 | |
| SUNBRIGHT ME-400TS | 40,000 | |

•SUNBRIGHT® NP Series (p-Nitrophenyl Carbonate PEG)



| Product name | MW | |
|--------------------|--------|--|
| SUNBRIGHT MENP-20H | 2,000 | |
| SUNBRIGHT MENP-50H | 5,000 | |
| SUNBRIGHT MENP-10T | 10,000 | |
| SUNBRIGHT MENP-20T | 20,000 | |
| SUNBRIGHT MENP-30T | 30,000 | |
| SUNBRIGHT MENP-40T | 40,000 | |

•SUNBRIGHT® AL Series (Aldehyde PEG)

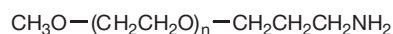


Exploiting our latest technologies, we supply mPEG-aldehydes without any reactive problematic impurities (e.g., bifunctional aldehydes).

当社は最新の技術を駆使し不純物である2官能性PEGを含まないmPEG-アルデヒドを製造しています。

| Product name | MW | |
|---------------------|--------|--|
| SUNBRIGHT ME-050AL | 5,000 | |
| SUNBRIGHT ME-100AL | 10,000 | |
| SUNBRIGHT ME-200AL | 20,000 | |
| SUNBRIGHT ME-300AL | 30,000 | |
| SUNBRIGHT ME-400AL2 | 40,000 | |

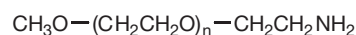
•SUNBRIGHT® PA Series (Aminopropyl PEG)



| Product name | MW |
|--------------------|--------|
| SUNBRIGHT MEPA-20H | 2,000 |
| SUNBRIGHT MEPA-50H | 5,000 |
| SUNBRIGHT MEPA-10T | 10,000 |
| SUNBRIGHT MEPA-12T | 12,000 |
| SUNBRIGHT MEPA-20T | 20,000 |
| SUNBRIGHT MEPA-30T | 30,000 |
| SUNBRIGHT MEPA-40T | 40,000 |

New

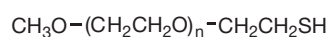
•SUNBRIGHT® EA Series (Aminoethyl PEG)



| Product name | MW |
|--------------------|--------|
| SUNBRIGHT ME-020EA | 2,000 |
| SUNBRIGHT ME-050EA | 5,000 |
| SUNBRIGHT ME-100EA | 10,000 |
| SUNBRIGHT ME-200EA | 20,000 |
| SUNBRIGHT ME-300EA | 30,000 |
| SUNBRIGHT ME-400EA | 40,000 |

New

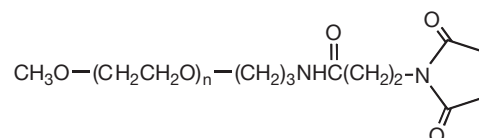
•SUNBRIGHT® SH Series (Thiol PEG)



| Product name | MW |
|--------------------|--------|
| SUNBRIGHT ME-020SH | 2,000 |
| SUNBRIGHT ME-050SH | 5,000 |
| SUNBRIGHT ME-100SH | 10,000 |
| SUNBRIGHT ME-200SH | 20,000 |
| SUNBRIGHT ME-300SH | 30,000 |
| SUNBRIGHT ME-400SH | 40,000 |

•SUNBRIGHT® MA Series (Maleimide PEG)

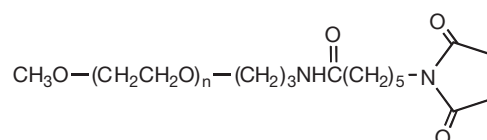
C2 Type



| Product name | MW |
|----------------------|--------|
| SUNBRIGHT ME-020MA | 2,000 |
| SUNBRIGHT ME-050MA | 5,000 |
| SUNBRIGHT ME-100MA | 10,000 |
| SUNBRIGHT ME-200MA0B | 20,000 |
| SUNBRIGHT ME-300MA | 30,000 |
| SUNBRIGHT ME-400MA | 40,000 |

New

※ Patent No. : US6875841

C5 Type **New**

| Product name | MW |
|----------------------|--------|
| SUNBRIGHT ME-050MA3* | 5,000 |
| SUNBRIGHT ME-100MA3* | 10,000 |
| SUNBRIGHT ME-200MA3* | 20,000 |
| SUNBRIGHT ME-400MA3* | 40,000 |

New

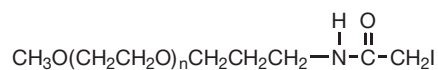
New

New

New

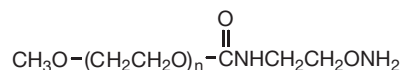
* : make-to-order

•SUNBRIGHT® IA series (Iodoacetamide PEG)



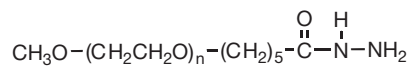
| Product name | MW |
|--------------------|--------|
| SUNBRIGHT ME-200IA | 20,000 |
| SUNBRIGHT ME-300IA | 30,000 |
| SUNBRIGHT ME-400IA | 40,000 |

•SUNBRIGHT® CA series (Aminoxy PEG)



| Product name | MW |
|--------------------|--------|
| SUNBRIGHT ME-100CA | 10,000 |
| SUNBRIGHT ME-200CA | 20,000 |
| SUNBRIGHT ME-300CA | 30,000 |
| SUNBRIGHT ME-400CA | 40,000 |

•SUNBRIGHT® HZ series (Hydrazide PEG)



| Product name | MW |
|---------------------|--------|
| SUNBRIGHT ME-200HZ* | 20,000 |
| SUNBRIGHT ME-300HZ* | 30,000 |
| SUNBRIGHT ME-400HZ* | 40,000 |

* : make-to-order

2. Bi-Functional PEGs

Bi-functional PEGs are the most popular derivatives for crosslinking proteins, enzymes and other pharmaceutical substance. Recently, these PEGs are applied for hydrogel components for base matrix of iPS cells or EPS cells in tissue engineering.

2官能 PEG は、通常、蛋白質等の架橋剤としてよく使用されています。近年ではその応用を生かしたハイドロゲルとして iPS 細胞等の再生医療分野で使用されています。また、ハイドロゲルの原料だけでなく、難溶性薬剤に応用することにより溶解性の向上が計れます。



| Product name | X | MW |
|---------------------|--|--------|
| NHS PEG | | |
| SUNBRIGHT DE-034CS* | Succinimidylsuccinate -CO-CH ₂ CH ₂ -COO-NHS | 3,400 |
| SUNBRIGHT DE-034GS* | Succinimidylglutarate -CO-CH ₂ CH ₂ CH ₂ COO-NHS | 3,400 |
| SUNBRIGHT DE-100GS | | 10,000 |
| SUNBRIGHT DE-200GS | | 20,000 |
| SUNBRIGHT DE-030AS* | Succinimidylcarboxymethyl -CH ₂ -COO-NHS | 3,000 |
| SUNBRIGHT DE-034HS* | Succinimidylcarboxypentyl -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -COO-NHS | 3,400 |
| SUNBRIGHT DE-100HS | | 10,000 |
| SUNBRIGHT DE-200HS | | 20,000 |
| Amine PEG | | |
| SUNBRIGHT DE-010PA | Propylamine -CH ₂ CH ₂ CH ₂ NH ₂ | 1,000 |
| SUNBRIGHT DE-020PA | | 2,000 |
| SUNBRIGHT DE-034PA* | | 3,400 |
| SUNBRIGHT DE-100PA | | 10,000 |
| SUNBRIGHT DE-200PA | | 20,000 |
| SUNBRIGHT DE-300PA | | 30,000 |
| Thiol PEG | | |
| SUNBRIGHT DE-034SH | Ethanethiol -CH ₂ CH ₂ SH | 3,400 |
| SUNBRIGHT DE-100SH* | | 10,000 |
| SUNBRIGHT DE-200SH* | | 20,000 |
| Maleimide PEG | | |
| SUNBRIGHT DE-100MA | Maleimide | 10,000 |
| SUNBRIGHT DE-200MA | -(CH ₂) ₃ -NHCO-CH ₂ CH ₂ -Maleimide | 20,000 |

* : make-to-order

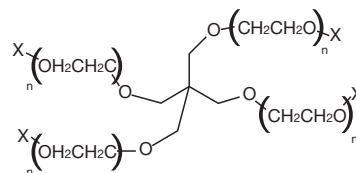
3. Multi-Arm PEGs

We supply various derivatives in which functional groups are attached to the terminals of multi-arm (4-arm and 8-arm) PEGs. Multi-arm PEGs can be used not only as the starting materials for hydrogels, but also as modifiers to improve the solubility of hydrophobic drugs.

4-アーム、8アームなど種々のマルチアームPEGの末端に、種々の官能性基を付与した誘導体製品を供給致しております。マルチアームPEGは、ハイドロゲルの原料だけでなく、難溶性薬剤に応用することにより溶解性の向上が計れます。

3-1. 4-arm-Functional PEG Series

PTE Series (Pentaerythritol, tetra-polyethylene glycol ether)

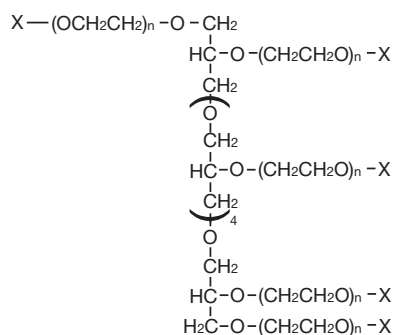


| Product name | X | MW |
|------------------------------------|--|--------|
| NHS PEG | | |
| SUNBRIGHT PTE-100CS | Succinimidylsuccinate -CO-CH ₂ CH ₂ -COO-NHS | 10,000 |
| SUNBRIGHT PTE-050GS* | | 5,000 |
| SUNBRIGHT PTE-100GS | | 10,000 |
| SUNBRIGHT PTE-150GS* | Succinimidylglutarate -CO-CH ₂ CH ₂ CH ₂ -COO-NHS | 15,000 |
| SUNBRIGHT PTE-200GS | | 20,000 |
| SUNBRIGHT PTE-400GS* | | 40,000 |
| SUNBRIGHT PTE-100HS* | | 10,000 |
| SUNBRIGHT PTE-200HS* | Succinimidylcarboxypentyl -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -COO-NHS | 20,000 |
| SUNBRIGHT PTE-400HS* | | 40,000 |
| p-Nitrophenyl carbonate PEG | | |
| SUNBRIGHT PTE-100NP | | 10,000 |
| SUNBRIGHT PTE-200NP | p-Nitrophenylcarbonate -COO-phenyl-NO ₂ | 20,000 |
| SUNBRIGHT PTE-400NP* | | 40,000 |
| Amine PEG | | |
| SUNBRIGHT PTE-100PA | | 10,000 |
| SUNBRIGHT PTE-150PA* | Propylamine -CH ₂ CH ₂ CH ₂ NH ₂ | 15,000 |
| SUNBRIGHT PTE-200PA | | 20,000 |
| SUNBRIGHT PTE-400PA* | | 40,000 |
| Thiol PEG | | |
| SUNBRIGHT PTE-050SH* | Ethanethiol -CH ₂ CH ₂ SH | 5,000 |
| SUNBRIGHT PTE-100SH | | 10,000 |
| SUNBRIGHT PTE-200SH | | 20,000 |
| Maleimide PEG | | |
| SUNBRIGHT PTE-100MA* | Maleimide | 10,000 |
| SUNBRIGHT PTE-200MA* | -(CH ₂) ₃ -NHCO-CH ₂ CH ₂ -Maleimide | 20,000 |
| SUNBRIGHT PTE-400MA* | | 40,000 |

* : make-to-order

3-2. 8-arm-Functional PEG Series

HGEO Series (Hexa-glycerine, octa-polyethylene glycol ether)



| Product name | X | MW |
|------------------------------------|---|--------|
| NHS PEG | | |
| SUNBRIGHT HGEO-150CS* | Succinimidylsuccinate -CO-CH ₂ CH ₂ -COO-NHS | 15,000 |
| SUNBRIGHT HGEO-150GS* | | 15,000 |
| SUNBRIGHT HGEO-200GS* | Succinimidylglutarate -CO-CH ₂ CH ₂ CH ₂ -COO-NHS | 20,000 |
| SUNBRIGHT HGEO-400GS* | | 40,000 |
| p-Nitrophenyl carbonate PEG | | |
| SUNBRIGHT HGEO-200NP* | p-Nitrophenylcarbonate | 20,000 |
| SUNBRIGHT HGEO-400NP* | -COO-phenyl-NO ₂ | 40,000 |
| Amine PEG | | |
| SUNBRIGHT HGEO-150PA* | Propylamine -CH ₂ CH ₂ CH ₂ NH ₂ | 15,000 |
| Thiol PEG | | |
| SUNBRIGHT HGEO-200SH* | Ethanethiol -CH ₂ CH ₂ SH | 20,000 |

* : make-to-order

4. Branched PEGs

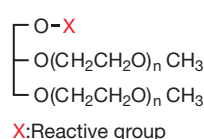
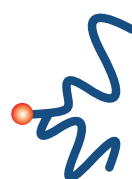
NOF provides 2-branched Activated PEGs, as illustrated below. Both the molecular weights of the respective PEG chains and the linker moieties leading to the functional groups are adjustable. These are available with amino, aldehyde, maleimide, carbonate and carboxylate activated esters as the terminal functional groups.

Furthermore, NOF has also developed newer types of Branched Activated PEGs, such as 3-branched and 4-branched derivatives. Although aqueous solutions of higher-molecular PEG derivatives tend to show increased viscosity, use of higher-branched Activated PEGs, such as 3-branched and 4-branched derivatives, reduces the viscosity of the relevant aqueous solutions, even without altering the molecular weights.

当社は、下記に示されるような2鎖分岐型 PEG 誘導体を開発しました。それぞれの PEG 鎖の分子量または官能基までのリンカー部分を調節することが出来ます。末端官能基としては、アミノ基、アルデヒド基、マレイミド基、カーボネート基、活性エステル化カルボキシル基を取り揃えております。

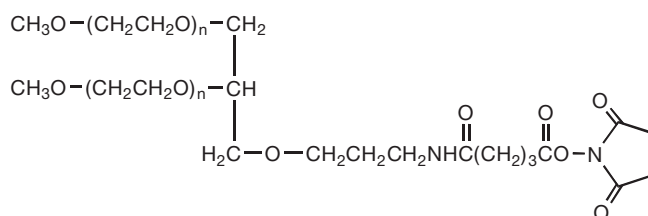
さらに、3鎖分岐型、4鎖分岐型といった新しい PEG 誘導体についても開発しています。高分子量の PEG 誘導体水溶液は粘性が高くなりますが、3鎖分岐型、4鎖分岐型と PEG 鎖の分岐数を増やすことにより、同分子量でも水溶液の粘性を低下させることができます。

4-1. 2-arm Branched PEG (SUNBRIGHT® GL2 series)



Total Mw 40kDa: 20k × 2
60kDa: 30k × 2
80kDa: 40k × 2

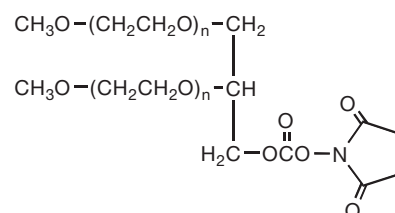
GS2 Type (NHS-ester PEG)



| Product name | MW |
|-----------------------|--------|
| SUNBRIGHT GL2-200GS2 | 20,000 |
| SUNBRIGHT GL2-400GS2 | 40,000 |
| SUNBRIGHT GL2-600GS2 | 60,000 |
| SUNBRIGHT GL2-800GS2* | 80,000 |

* : make-to-order

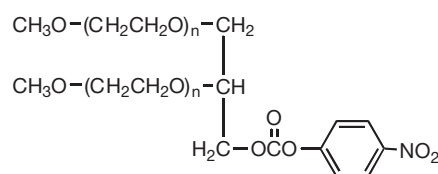
TS Type (NHS Carbonate PEG)



| Product name | MW |
|----------------------|--------|
| SUNBRIGHT GL2-200TS | 20,000 |
| SUNBRIGHT GL2-400TS | 40,000 |
| SUNBRIGHT GL2-600TS | 60,000 |
| SUNBRIGHT GL2-800TS* | 80,000 |

* : make-to-order

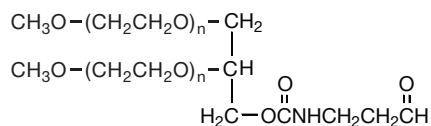
NP Type (P-Nitrophenyl Carbonate PEG)



| Product name | MW |
|----------------------|--------|
| SUNBRIGHT GL2-100NP | 10,000 |
| SUNBRIGHT GL2-200NP | 20,000 |
| SUNBRIGHT GL2-400NP | 40,000 |
| SUNBRIGHT GL2-600NP | 60,000 |
| SUNBRIGHT GL2-800NP* | 80,000 |

* : make-to-order

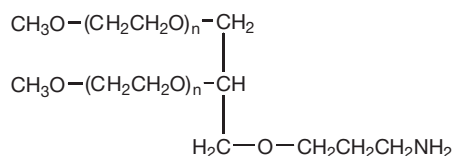
AL3 Type (Aldehyde PEG)



| Product name | MW |
|-----------------------|--------|
| SUNBRIGHT GL2-200AL3 | 20,000 |
| SUNBRIGHT GL2-400AL3 | 40,000 |
| SUNBRIGHT GL2-600AL3 | 60,000 |
| SUNBRIGHT GL2-800AL3* | 80,000 |

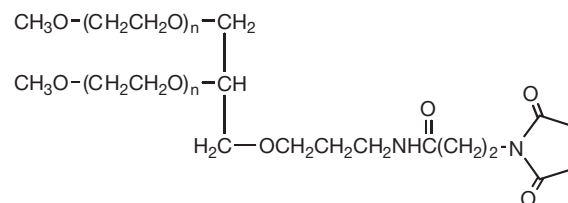
*: make-to-order

PA Type (Aminopropyl PEG)

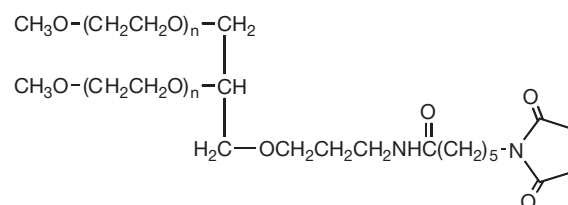


| Product name | MW |
|---------------------|--------|
| SUNBRIGHT GL2-200PA | 20,000 |
| SUNBRIGHT GL2-400PA | 40,000 |
| SUNBRIGHT GL2-600PA | 60,000 |
| SUNBRIGHT GL2-800PA | 80,000 |

C2 MA Type (Maleimide PEG)



| Product name | MW |
|---------------------|--------|
| SUNBRIGHT GL2-200MA | 20,000 |
| SUNBRIGHT GL2-400MA | 40,000 |
| SUNBRIGHT GL2-600MA | 60,000 |
| SUNBRIGHT GL2-800MA | 80,000 |

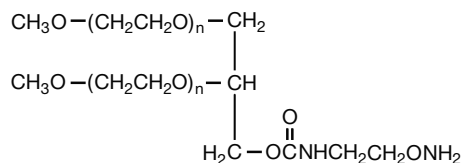
C5 MA Type (Maleimide PEG) **New**

| Product name | MW |
|-----------------------|--------|
| SUNBRIGHT GL2-400MA3* | 40,000 |

New

*: make-to-order

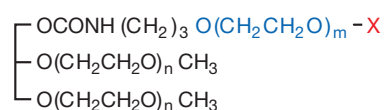
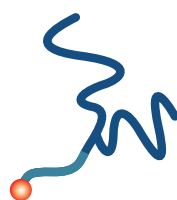
CA Type (Aminoxy PEG)



| Product name | MW |
|----------------------|--------|
| SUNBRIGHT GL2-100CA* | 10,000 |
| SUNBRIGHT GL2-200CA | 20,000 |
| SUNBRIGHT GL2-400CA | 40,000 |
| SUNBRIGHT GL2-600CA* | 60,000 |
| SUNBRIGHT GL2-800CA* | 80,000 |

*: make-to-order

4-2. 3-arm Branched PEG (SUNBRIGHT® GL3 series)

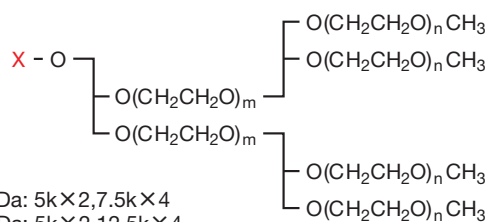
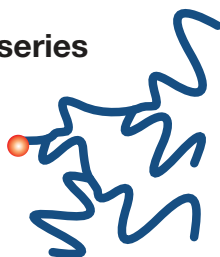


Total Mw 50kDa
Mw of (CH₂CH₂O)_m part :about 10kDa

| Product name | X | MW |
|------------------------------------|--|--------|
| NHS PEG | | |
| SUNBRIGHT GL3-400GS100U | Succinimidylglutarate -CO-CH ₂ CH ₂ CH ₂ -COO-NHS | 50,000 |
| SUNBRIGHT GL3-400HS100U | Succinimidylcarboxypentyl -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -COO-NHS | 50,000 |
| SUNBRIGHT GL3-400TS100U | Succinimidylcarboxy -COO-NHS | 50,000 |
| p-Nitrophenyl carbonate PEG | | |
| SUNBRIGHT GL3-400NP100U | p-Nitrophenylcarbonate -COO-phenyl-NO ₂ | 50,000 |
| Aldehyde PEG | | |
| SUNBRIGHT GL3-400AL100U | Aldehyde -CH ₂ -CH ₂ -CHO | 50,000 |
| Amine PEG | | |
| SUNBRIGHT GL3-400PA100U | Propylamine -CH ₂ CH ₂ CH ₂ NH ₂ | 50,000 |
| Maleimide PEG | | |
| SUNBRIGHT GL3-400MA100U | Maleimide -(CH ₂) ₃ -NHCO-CH ₂ CH ₂ -maleimide | 50,000 |
| Aminoxy PEG | | |
| SUNBRIGHT GL3-400CA100U | Aminoxy -CONH-CH ₂ CH ₂ -ONH ₂ | 50,000 |

4-3. 4-arm Branched PEG

1) SUNBRIGHT® GL4 series

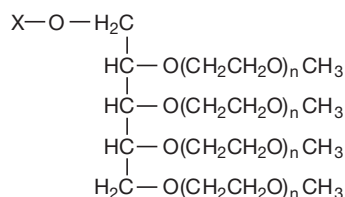


Total Mw 40kDa: $5\text{k} \times 2, 7.5\text{k} \times 4$
 60kDa: $5\text{k} \times 2, 12.5\text{k} \times 4$
 80kDa: $5\text{k} \times 2, 17.5\text{k} \times 4$

| Product name | X | MW |
|-----------------------------|---|--------|
| NHS PEG | | |
| SUNBRIGHT GL4-400GS2 | Succinimidylglutarate-aminopropoxy -CH ₂ CH ₂ CH ₂ -NHCO-(CH ₂) ₃ -COO-NHS | 40,000 |
| SUNBRIGHT GL4-600GS2* | | 60,000 |
| SUNBRIGHT GL4-800GS2* | | 80,000 |
| SUNBRIGHT GL4-400TS | Succinimidylcarboxy -COO-NHS | 40,000 |
| SUNBRIGHT GL4-600TS* | | 60,000 |
| SUNBRIGHT GL4-800TS* | | 80,000 |
| p-Nitrophenyl carbonate PEG | | |
| SUNBRIGHT GL4-400NP | p-Nitrophenylcarbonate -COO-phenyl-NO ₂ | 40,000 |
| SUNBRIGHT GL4-600NP* | | 60,000 |
| SUNBRIGHT GL4-800NP* | | 80,000 |
| Aldehyde PEG | | |
| SUNBRIGHT GL4-400AL3 | Aldehyde -CONH-CH ₂ CH ₂ -CHO | 40,000 |
| SUNBRIGHT GL4-600AL3* | | 60,000 |
| SUNBRIGHT GL4-800AL3* | | 80,000 |
| Amine PEG | | |
| SUNBRIGHT GL4-400PA | Propylamine -CH ₂ CH ₂ CH ₂ NH ₂ | 40,000 |
| SUNBRIGHT GL4-600PA* | | 60,000 |
| SUNBRIGHT GL4-800PA* | | 80,000 |
| Maleimide PEG | | |
| SUNBRIGHT GL4-400MA | Maleimide -(CH ₂) ₃ -NHCO-CH ₂ CH ₂ -maleimide | 40,000 |
| SUNBRIGHT GL4-600MA* | | 60,000 |
| SUNBRIGHT GL4-800MA* | | 80,000 |
| Aminoxy PEG | | |
| SUNBRIGHT GL4-400CA | Aminoxy -CONH-CH ₂ CH ₂ -ONH ₂ | 40,000 |
| SUNBRIGHT GL4-600CA* | | 60,000 |
| SUNBRIGHT GL4-800CA* | | 80,000 |

* : make-to-order

2) SUNBRIGHT® XY4 series New



| Product name | X | MW | |
|------------------------------------|---|--------|--------------------------------------|
| NHS PEG | | | |
| SUNBRIGHT XY4-200GS2* | Succinimidylglutarate-aminopropoxy | 20,000 | New |
| SUNBRIGHT XY4-400GS2 | -CH ₂ CH ₂ CH ₂ -NHCO-(CH ₂) ₃ -COO-NHS | 40,000 | New |
| SUNBRIGHT XY4-200TS* | Succinimidylcarboxy | 20,000 | New |
| SUNBRIGHT XY4-400TS | -COO-NHS | 40,000 | New |
| p-Nitrophenyl carbonate PEG | | | |
| SUNBRIGHT XY4-200NP* | p-Nitrophenylcarbonate | 20,000 | New |
| SUNBRIGHT XY4-400NP | -COO-phenyl-NO ₂ | 40,000 | New |
| Aldehyde PEG | | | |
| SUNBRIGHT XY4-200AL3* | Aldehyde | 20,000 | New |
| SUNBRIGHT XY4-400AL3 | -CONH-CH ₂ CH ₂ -CHO | 40,000 | New |
| Maleimide PEG | | | |
| SUNBRIGHT XY4-200MA* | Maleimide | 20,000 | New |
| SUNBRIGHT XY4-400MA | -(CH ₂) ₃ -NHCO-CH ₂ CH ₂ -maleimide | 40,000 | New |

* : make-to-order

Comparison Data of PEG-Solution Viscosity

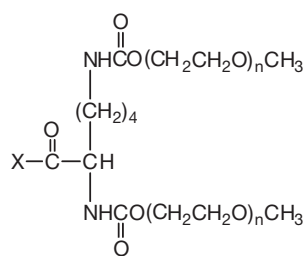
| Compound | Structure | Viscosity (mPa · s) |
|-----------------|-----------|---------------------|
| MeO-PEG (40kDa) | Linear | 19.3 |
| GL2 (40kDa) | 2-arm | 18.8 |
| GL4 (40kDa) | 4-arm | 10.9 |
| XY4 (40kDa) | 4-arm | 9.6 |

※ as aqueous solution at 10 wt%, at 40°C

4-4. Lysine Branched PEG New (SUNBRIGHT® LY series)

Collaborating with Enzon Pharmaceuticals, Inc., NOF has a right to manufacture and sell their unique Lysine Branched PEG (NOF's Trade Name is SUNBRIGHT LY series) for customer research purpose only. Lysine Branched PEG has been already used in several marketed PEGylated-drugs such as PEGASIS®, MACUGEN® and CIMZIA® for 10 years.

リジン分岐 PEG は、すでにさまざまな PEG 化製剤に使用されている実績の高い活性化 PEG です。日油と ENZON 社は契約を締結し、ENZON 社の特殊活性化 PEG を販売することができるようになりました。



| Product name | X | MW | |
|----------------------|--|--------|--------------------------------------|
| NHS PEG | | | |
| SUNBRIGHT LY-400NS | Succinimidyl ester -O-NHS | 40,000 | New |
| Aldehyde PEG | | | |
| SUNBRIGHT LY-400AL3* | Aldehyde -NH-CH ₂ CH ₂ -CHO | 40,000 | New |
| Maleimide PEG | | | |
| SUNBRIGHT LY-400MA* | Maleimide -NH(CH ₂) ₂ -NHCO-(CH ₂) ₂ -maleimide | 40,000 | New |

* : make-to-order

※ The Lysine Branched PEG belong to ENZON Pharmaceuticals, Inc., is sold by NOF for research and development purpose only.

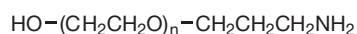
5. Heterofunctional PEGs

X-(OCH₂CH₂)_n-Y

By using hetero-type activated PEGs, different molecules can be conjugated onto the each end of the PEGs. They are also useful for surface modification.

ヘテロタイプの活性化 PEG は、両末端にそれぞれ異なる分子を導入することができます。表面修飾にも有用です。

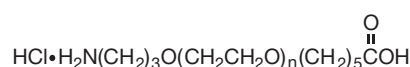
•Hydroxy-PEG-Amine



| Product name | MW |
|---------------------|--------|
| SUNBRIGHT HO-020PA | 2,000 |
| SUNBRIGHT HO-034PA | 3,400 |
| SUNBRIGHT HO-050PA | 5,000 |
| SUNBRIGHT HO-100PA | 10,000 |
| SUNBRIGHT HO-200PA | 20,000 |
| SUNBRIGHT HO-400PA* | 40,000 |

* : make-to-order

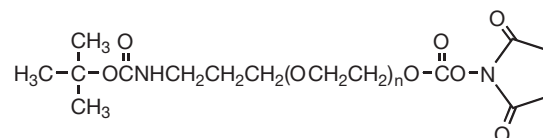
•Amino-PEG-Carboxylic acid



| Product name | MW |
|---------------------|-------|
| SUNBRIGHT PA-020HC* | 2,000 |
| SUNBRIGHT PA-034HC* | 3,400 |
| SUNBRIGHT PA-050HC* | 5,000 |

* : make-to-order

•Boc-protected-Amino-PEG-Carbonate-NHS

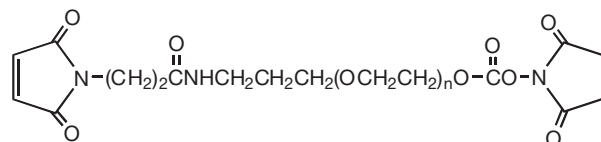


| Product name | MW |
|---------------------|--------|
| SUNBRIGHT BO-020TS* | 2,000 |
| SUNBRIGHT BO-034TS* | 3,400 |
| SUNBRIGHT BO-050TS* | 5,000 |
| SUNBRIGHT BO-100TS* | 10,000 |
| SUNBRIGHT BO-200TS* | 20,000 |

New

* : make-to-order

•Maleimide-PEG-Carbonate-NHS

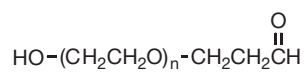


| Product name | MW |
|---------------------|--------|
| SUNBRIGHT MA-020TS* | 2,000 |
| SUNBRIGHT MA-034TS* | 3,400 |
| SUNBRIGHT MA-050TS* | 5,000 |
| SUNBRIGHT MA-100TS* | 10,000 |
| SUNBRIGHT MA-200TS* | 20,000 |
| SUNBRIGHT MA-400TS* | 40,000 |

New

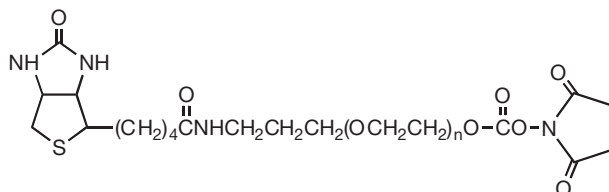
* : make-to-order

•Hydroxy-PEG-Aldehyde



| Product name | MW |
|--------------------|--------|
| SUNBRIGHT HO-050AL | 5,000 |
| SUNBRIGHT HO-100AL | 10,000 |
| SUNBRIGHT HO-200AL | 20,000 |
| SUNBRIGHT HO-300AL | 30,000 |

•Biotin-PEG-Carbonate-NHS



| Product name | MW |
|---------------------|-------|
| SUNBRIGHT BI-050TS* | 5,000 |

* : make-to-order

6. Forked PEGs New

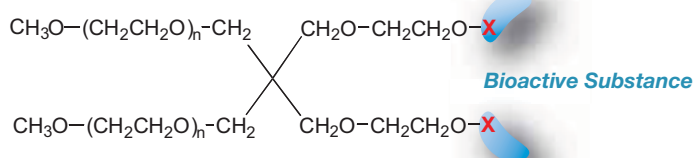
•SUNBRIGHT® PTE2 Series

Forked structures have the advantage of placing two reactive groups at precise distances apart. These "Forked" PEGs have become very popular for mimicking the heavy chain domain in an antibody or fragment antibody and other applications where two proteins held in proximity are advantageous.

1つの活性化PEGが2つの官能基をもち、薬剤を2つ結合させることで薬剤の効果を上げることが期待されます。

日油は隣接する官能基を2つ持つ活性化PEGをご提供できるようになりました。

抗体医薬のドメインや抗体フラグメントのPEG化では特に有用で、すでにいろいろな応用が確認されています。



| Product name | X | MW | |
|------------------------|---|--------|--------------------------------------|
| NHS PEG | | | |
| SUNBRIGHT PTE2-200GS3* | Succinimidyl ester | 20,000 | New |
| SUNBRIGHT PTE2-400GS3* | -CH ₂ CH ₂ -NHCO-(CH ₂) ₃ -COO-NHS | 40,000 | New |
| Amine PEG | | | |
| SUNBRIGHT PTE2-200EA* | Ethylamine | 20,000 | New |
| SUNBRIGHT PTE2-400EA* | -CH ₂ CH ₂ NH ₂ | 40,000 | New |
| Maleimide PEG | | | |
| SUNBRIGHT PTE2-200MA2* | Maleimide | 20,000 | New |
| SUNBRIGHT PTE2-400MA2* | -CH ₂ CH ₂ -NHCO-(CH ₂) ₂ -maleimide | 40,000 | New |

* : make-to-order

7. Releasable PEGs New

•SUNBRIGHT® BE-Linker series

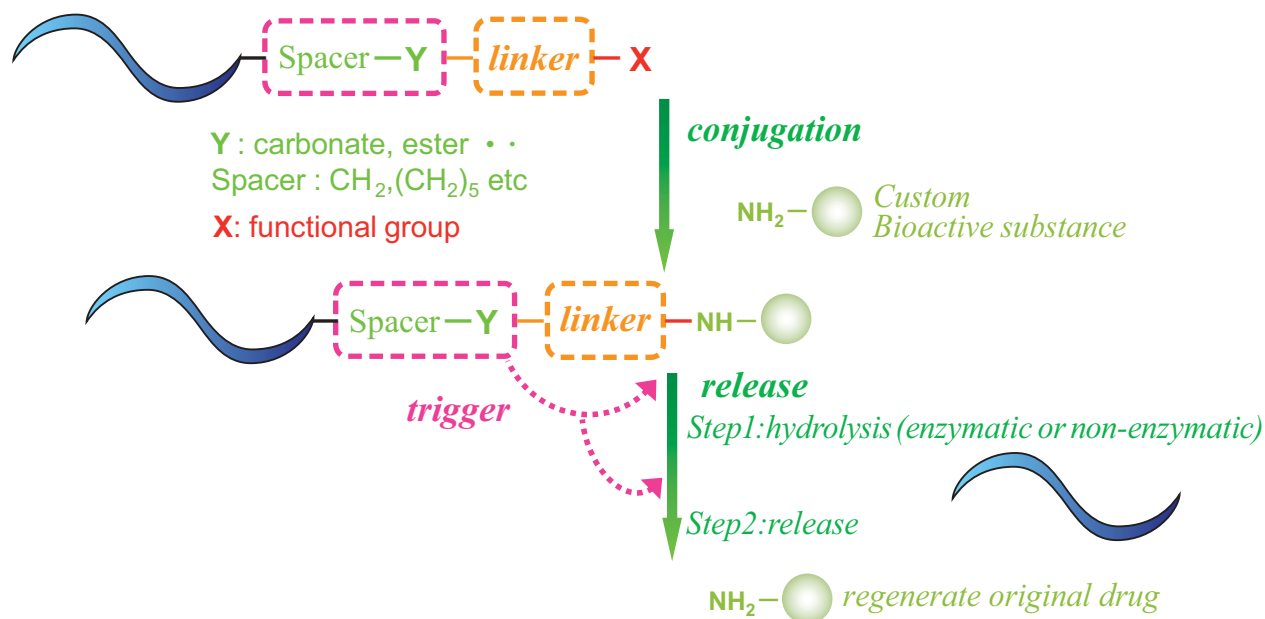
Pegylated therapeutic protein or small molecule pharmacology would be substantially expanded if the original therapeutic proteins or small molecules could be regenerated in vivo. Diminution of activity of both enzymes and protein ligands is commonly encountered following permanent conjugation with polyethylene glycol (PEG). However, Enzon's releasable PEG linkers have the ability to improve the pharmaceutical properties of therapeutic proteins or small molecules through releasable PEGylation and maintain the therapeutic effect of these molecules by regenerating the bioactive proteins or small molecules in vivo. To make available Enzon's releasable linker technology, NOF introduces the Benzyl Elimination (BE) linkers, i.e. PEG-BE-NHS, SUNBRIGHT BE Series, as listed in the following.

PEG 化した薬剤は、投与されたあとに生体内でフリーの薬物として放出されると、更に利用用途が広がると考えられています。薬物とリガンドとの親和性は、PEG 鎖が結合することにより、一般的には弱まる現象が見られます。しかし、Enzon 社が開発したリリーサブル PEG(放出型リンカーを含む活性化 PEG)を用いた PEG 化製剤においては、生体内で薬物を放出することにより、これら薬物の効果を維持し、製剤としての性能を高めることが可能になります。Enzon 社のリリーサブルリンカー技術の一つとして SUNBRIGHT BE シリーズについて紹介します。

The advantage of SUNBRIGHT® BE series:

- Controls pharmacokinetics of drugs in vivo (C_{max} , T_{max} , $T_{1/2}$)
- Provides high loading capability
- Deposits poorly soluble drugs at target tissue
- Customized cellular uptake, trafficking and processing

Releasing drug from PEG-drug conjugates (NOF SUNBRIGHT® BE-Linker series)



| Product name | Chemical structure | MW | |
|---------------------------|--------------------|--------|--------------------------------------|
| SUNBRIGHT ME-BE200CH-TS* | | 20,000 | New |
| SUNBRIGHT ME-BE200CM-TS* | | 20,000 | New |
| SUNBRIGHT ME-BE200EH5-TS* | | 20,000 | New |
| SUNBRIGHT ME-BE200EM5-TS* | | 20,000 | New |

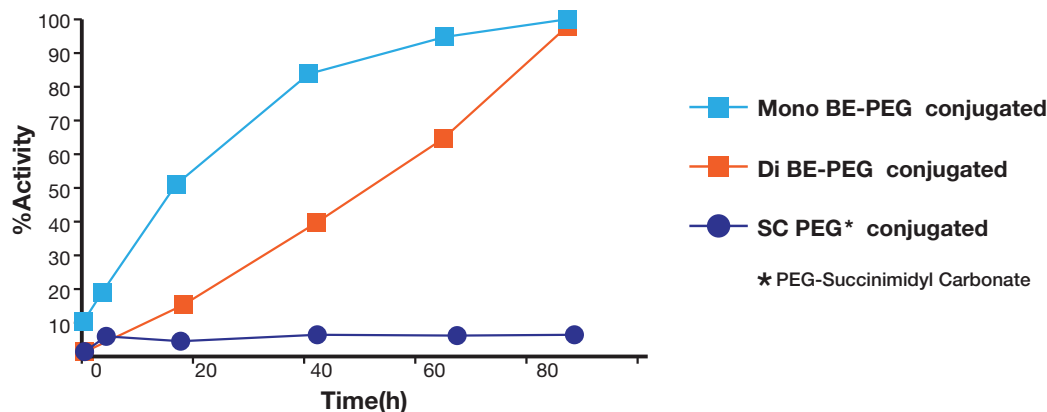
※ The Releasable Activated PEG belong to ENZON Pharmaceuticals Inc., is sold by NOF for research and development purpose only.

※ Orders for other molecular weights and linkers may require custom synthesis. Please e-mail at ddsinfo@nof.co.jp for a quote on custom reagents.

* : make-to-order

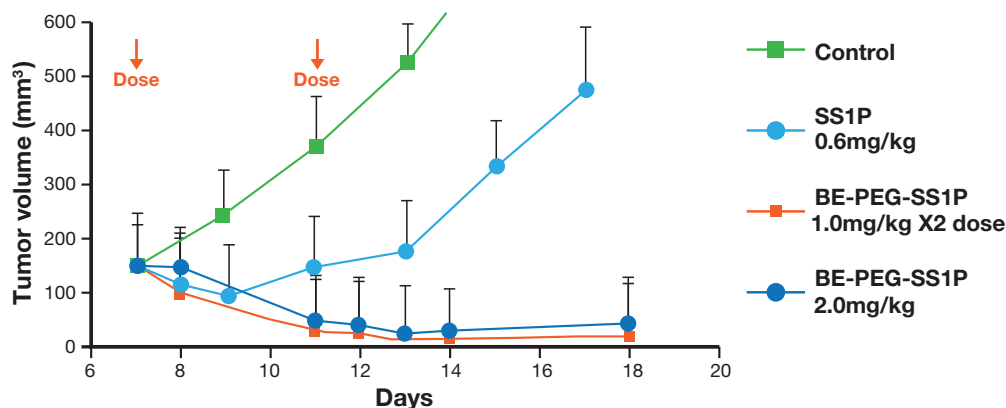
Characteristics of SUNBRIGHT® BE-Linker

•Effects of PEG-BE Linker on Lysozyme Regeneration



Regeneration of lysozyme from PEG-BE-lysozyme conjugates in rat plasma.
S Lee, et al., *Bioconjugate Chem.* **12(2)**, 163-169 (2001)

•Antitumor effects of PEG-BE-immunotoxin (BE-PEG-SS1P)



Antitumor effects of PEG-BE-SS1P and SS1P on A431-K5 solid tumors.
Cells (3×10^6) were injected s.c. into nude mice on day 0. On day 7 (tumor volume = $\sim 140 \text{ mm}^3$), animals were treated with i.v. injections of the compounds at the indicated doses. Control mice received vehicle only.
D Filpula, et al., *Bioconjugate Chem.* **18(3)**, 773-784 (2007)

•Hydrolysis, Cytotoxicity, Antitumor activity of PEG-BE-Daunorubicin

| Compound | $t_{1/2}(\text{hr})$ buffer (pH 7.4) | $t_{1/2}(\text{hr})$ rat plasma | IC ₅₀ * ¹ (nM) p388/0 | Antitumor * ² i.v. % T/C * ³ |
|--|--|---------------------------------------|---|--|
| Daunorubicin (DNR) | control | control | 3 | 117.0 |
| Esters $\text{PEG}-\text{C}(=\text{O})-\text{O}-\text{C}_6\text{H}_3(\text{R}_1, \text{R}_2)-\text{CH}_2\text{O}-\text{C}(=\text{O})-\text{NH}-\text{DNR}$ $\text{R}_1 = \text{R}_2 = \text{H}$ $\text{R}_1 = \text{R}_2 = \text{OCH}_3$ $\text{R}_1 = \text{R}_2 = \text{CH}_3$ | >24 | 0.4 | 8 | NA |
| | >48 | 1.0 | 27 | 48.2 |
| | >48 | 1.9 | 55 | 67.9 |
| Carbonates $\text{PEG}-\text{O}-\text{C}(=\text{O})-\text{O}-\text{C}_6\text{H}_3(\text{CH}_3)_2-\text{CH}_2\text{O}-\text{C}(=\text{O})-\text{NH}-\text{DNR}$ | >48 | 2.9 | 179 | 74.4 |

*¹ : Half maximal (50%) inhibitory concentration, Inhibition of P388 leukemia

*² : 3 mg/kg/dose of DNR to BALB/c mice bearing subcutaneous Madison lung carcinoma(M-109) on days 1 and 4(ip) / 3 and 6(iv).

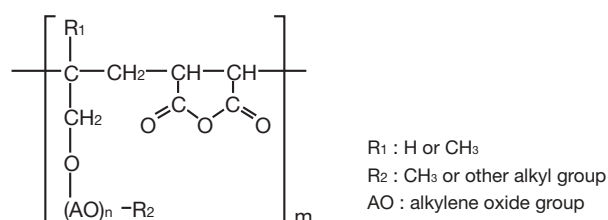
*³ : Percent treatment over control (%T/C)

RB Greenwald et al., *J. Med. Chem.* **42**, 3657-3667 (1999)

8. Comb-shaped co-polymers (carboxylic anhydride type)

When these reactive polymers are used for modification of enzymes, less reactivity is required to introduce more PEG chains onto the enzyme surfaces than that of a single polymeric PEG modifier. Consequently, the activities of the modified enzymes can be improved.

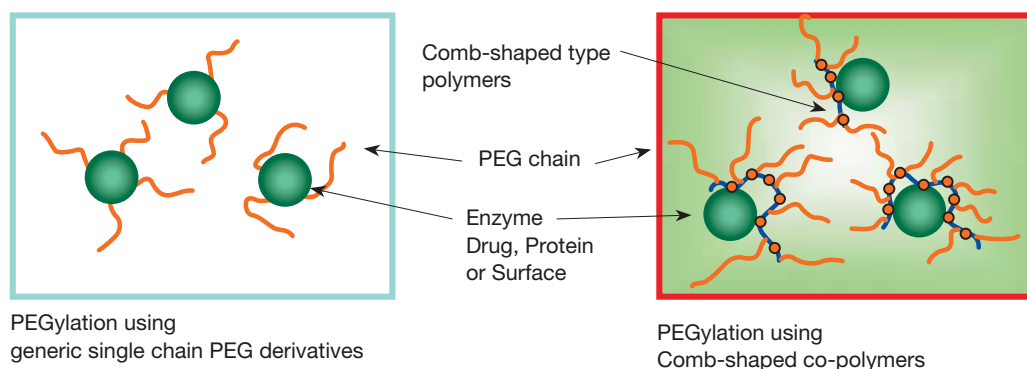
このポリマーを酵素の修飾に用いますと、一本鎖のPEG修飾剤を用いた場合に比べて、少ない結合で酵素表面により多くのPEG鎖を導入することができます。その結果、修飾酵素の残存活性が高くなります。



General Characteristics of PEG SUNBRIGHT® AM series

| Product Name | MW of AO (PEG) | DP ⁽¹⁾ | Total MW |
|--------------------|----------------|-------------------|---------------------|
| SUNBRIGHT AM-0530K | ca. 500 | ca. 30 ~ 40 | ca. 15,000 ~ 20,000 |
| SUNBRIGHT AM-1510K | ca. 1,500 | ca. 10 ~ 15 | ca. 15,000 ~ 20,000 |
| SUNBRIGHT AM-2090P | ca. 2,000 | ca. 10 ~ 20 | ca. 20,000 ~ 40,000 |

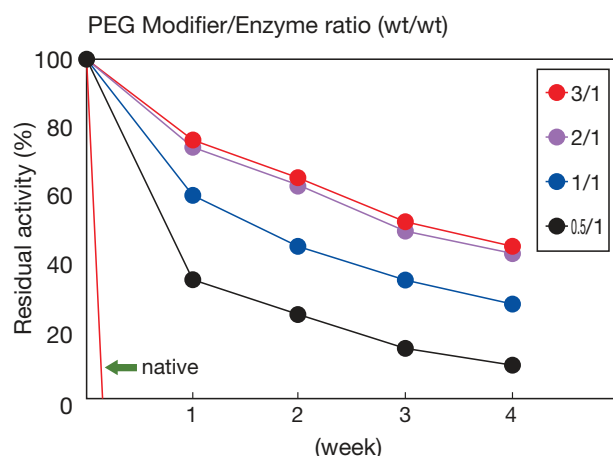
(1) Degree of Polymerization



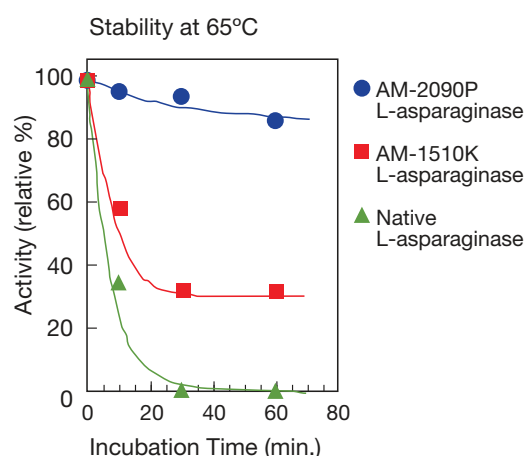
Moreover, with the use of this compound, the hydrophilic/lipophilic balance can be adjusted by changing the composition ratios of the ethylene oxide and propylene oxide in the polyalkylene glycol present in this compound.

さらにこの化合物は、骨格内のポリアルキレングリコールのエチレンオキシドとプロピレンオキシドの組成比を変えることにより、親水性・親油性のバランスを調整することができます。使用する酵素に応じて最適なポリマーを選択することにより、修飾酵素を有機溶剤に溶解することも可能です。

Efficacy of Comb-type PEG Enzyme Conjugation Stability of Modified Protease in water (at 40°C)



Stability of modified L-Asparaginase



References: for modified enzymes using SUNBRIGHT AM-series:

- 1) J. Kajiuchi et al., *J. Chem. Eng. Japan* **25**, 202 (1992)
- 2) T. Masunaga, et al., *J. SCCJ* **27(3)**, 276 (1993)
- 3) H. Sasaki et al., *Biochem. Biophys. Res. Commun* **197**, 287 (1993)
- 4) Y. Kodera, et al., *Bioconjugate Chem.* **5**, 283 (1994)
- 5) K. Matsuo, et al., *Adv. Bioseparation Eng.* 1993 **3**, 56 (1994)

III

Phospholipids and Lipids for Liposomal Formulations <COATSOME® Series>

Using the latest synthetic and purification technologies, NOF manufactures and supplies highly purified phospholipid derivatives (COATSOME Series) suitable for lipid emulsion formulations and liposome formulations which are extensively used for pharmaceuticals and cosmetics. Various kinds and grades of such phospholipids are readily available. In addition, we can respond to requests from our customers with tailor-made synthesis of any phospholipid with the desired structures. To benefit easy liposomal capture of drugs at customer facilities, NOF provides empty liposome kits, liposomal formulations and liposomal drug delivery systems.

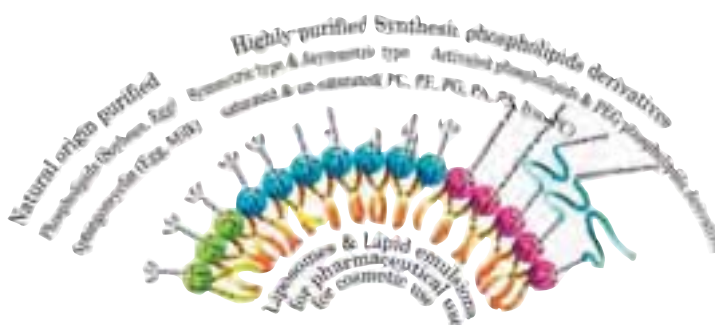
When PEGylated phospholipids are used as liposomes, the aqueous corona at the liposome surface facilitates stable dispersion in aqueous solutions.

当社は、医薬品や化粧品などの脂肪乳剤処方やリポソーム処方に適した高純度リン脂質誘導体 (COATSOME シリーズ) を、世界トップレベルの最新合成技術・精製技術を用いて提供しています。医薬・化粧品用リン脂質については豊富な品種とグレードを取り揃えています。また、お客様の要望にあわせた構造のリン脂質についてもカスタム合成いたします。さらに、簡単に薬剤のリポソーム化ができる中空リポソームキットやリポソーム処方液、リポソーム製造機も販売しています。

リン脂質と PEG を結合させた PEG-リン脂質をリポソームに用いることにより、リポソーム表面に水和層を付加することができます。薬剤等を内包したリポソーム製剤を安定に分散させることができます。



Liposomes were imaged by FEI Ltd., using Cryo-TEM (TECNAI F20TWIN Cryo).



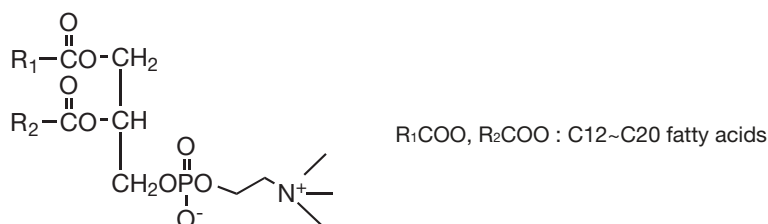
NOF Phospholipid Product Summary

1. Purified Phospholipids from natural sources

1-1. Soybean Phospholipids

NOF manufactures high-purity lecithin containing higher contents of phosphatidylcholine by using strictly selected natural soybeans uncontaminated with genetically modified soybeans. The high-purity product is useful to obtain favorable color and odor of the final product. What is more, the less unsaturated double-bonds in the acyl chains from higher hydrogenation result in excellent stability, together with easier handling of this lecithin in its powder form.

遺伝子組換え原料を使用していない厳選された天然大豆を原料に用いて、ホスファチジルコリン含量の高い高純度なレシチンを提供しています。高純度品であるため、色や臭いに優れていて、水素添加によりアシル鎖の不飽和基を少なくしていますので、非常に安定性に優れ、粉末形態であるため使いやすくなっています。

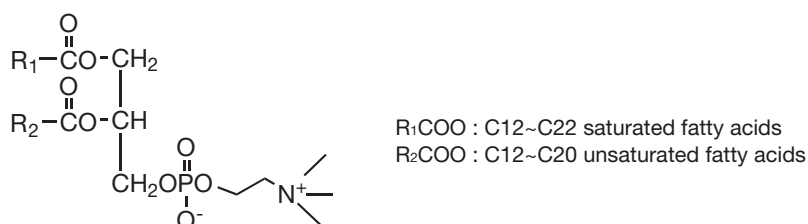


| | Product Name | Description | PC purity | MW |
|-------------|-----------------|--|-----------|--------|
| HSPC | COATSOME NC-21E | Hydrogenated Soybean phosphatidylcholine | 98% up | Ca.785 |
| HSPC | COATSOME NC-21 | Hydrogenated Soybean phosphatidylcholine | 90% up | Ca.785 |

1-2. Egg yolk Phospholipids

Egg yolk phospholipids are manufactured using virusfree yolk as the starting material, followed by removal of impurities through strict purification procedures. Unique NOF advantages include major phospholipids containing two different acyl groups (saturated and unsaturated fatty acids) in the same molecule. These unique chemical structures provide excellent dispersing ability in aqueous solution and favorable surfactant effects. Egg yolk phospholipids are also employed as carriers for lipophilic drugs as one of the major ingredients of lipid microspheres.

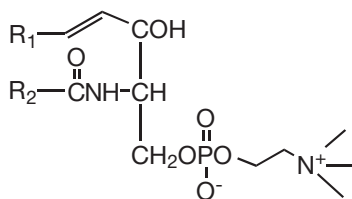
ウィルスフリーの卵黄を原料として、高度精製して不純物を除去しています。卵黄リン脂質の特徴は、リン脂質中の二つのアシル基がそれぞれ飽和と不飽和と異なっている構造のリン脂質が主成分であることです。そのため、水分散性が良く界面活性に優れています。また、リポドマイクロスフェアの主要構成成分の一つとして、親油性薬物のキャリアーに用いられています。



| | Product Name | Description | PC purity | MW |
|-------------|----------------|--|-----------|--------|
| EPC | COATSOME NC-50 | Non-hydrogenated Egg phosphatidylcholine | 95% up | Ca.773 |
| HEPC | COATSOME NC-11 | Hydrogenated Egg phosphatidylcholine | 95% up | Ca.777 |

1-3. Sphingomyelin

Phospholipids are known to be the primary constituents of biological membranes. Recently, however, it has been clarified that phospholipids are not only constituents of the cell membrane, but also play important direct roles in the cell membrane functions. Among the phospholipids, sphingomyelin has been revealed to be significantly important in both the formation and maintenance of lipid rafts. Considering that the lipid rafts have been shown to be involved in various signaling pathways, including immunological responses and transportation of specific materials, sphingomyelin has drawn much attention as a substance with important roles in the expression of specific cellular functions, such as intracellular information transmission and maintenance of membrane structure. Despite containing long fatty acid chains, sphingomyelin exhibits some advantageous characteristics such as a low phase-transition temperatures (T_c), that render it uniquely suitable for liposomal formations. NOF supplies high-purity sphingomyelin derived from milk and egg yolk. Concerning yolk-derived sphingomyelin, palmitic acid accounts for about 80% of the fatty acid chains bound by amide bonds; in sharp contrast, however, milk-derived sphingomyelin contains a broader range of long-chain fatty acids, including palmitic acid or longer-chain fatty acids. Because of these differences in the physical properties, customers can select between the two sources depending on their needs.



リン脂質は、生体膜を構成する主要な物質ですが、近年、これらの脂質が構成脂質の役割にとどまらず、膜機能に直接関与する重要な役割を担っていることがわかってきました。中でも、スフィンゴミエリンは、ラフトの形成と維持に非常に重要であることが明らかにされています。ラフトは、免疫応答を始めさまざまなシグナリングの場として、また特定の物質輸送の場として機能していて、スフィンゴミエリンが、生体膜の構造維持とともに細胞内情報伝達系への関与など細胞の機能発現にも大きく関わる物質として大変注目されています。またスフィンゴミエリンは脂肪酸鎖長が長い割に、相転移温度(T_c)が低いという特徴があり、リポソーム化しやすい基剤です。

当社は注目度の高いスフィンゴミエリンを牛乳由来のものと卵黄由来のものを高度精製して提供します。

卵黄由来では、アミド結合した脂肪酸鎖の約80%がパルミチン酸であるのに対し、牛乳由来では、パルミチン酸以上の長鎖の脂肪酸が幅広く含まれていて、物理的な性質が若干異なるので、用途に応じて選択できます。

| | Product Name | Description | Purity | MW | Alkyl composition |
|-----------------|----------------|--------------------|--------|----------|--|
| Egg-SPM | COATSOME NM-10 | Egg-Sphingomyelin | 98% up | Ca.703 | R ₁ : C13 R ₂ : C15:0, C17:0 |
| Milk-SPM | COATSOME NM-70 | Milk-Sphingomyelin | 98% up | Ca.779.5 | R ₁ : C13-C24 R ₂ : C15:0, C17:0, C21:0, C22:0, C23:0 |

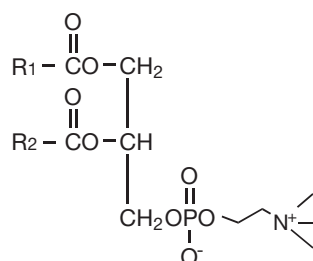
2. Highly-purified Synthetic Phospholipids

We use fatty acids that are highly purified by our own technologies for the manufacture of a variety of phospholipid derivatives; that is, NOF can synthesize derivatives containing a variety of fatty acids. Our phospholipids are manufactured in FDA-inspected facilities meeting GMP standards. Our quality-assured products can be safely used for the production of pharmaceuticals. NOF as a contracted manufacturer also synthesizes novel phospholipid derivatives and has completed DMF registrations for numerous novel derivatives; we are in a position to supply relevant lipids from test reagent grade to commercial production scales that are approved for manufacture of pharmaceuticals after clinical studies.

原料の脂肪酸を自社で高純度に精製して、各種リン脂質誘導体を製造していますので、様々な脂肪酸組成の誘導体を合成することができます。当社の合成リン脂質は、FDA の認可を受けた GMP 管理下の工場で製造していますので、安心して医薬品に使うことが出来ます。

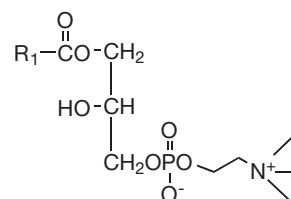
新しいリン脂質誘導体についても受託合成致し、新規誘導体の DMF 登録も数多く行っていますので、試薬ステージから臨床ステージ、さらには承認医薬品用途まで供給できます。

2-1. Phosphatidylcholine



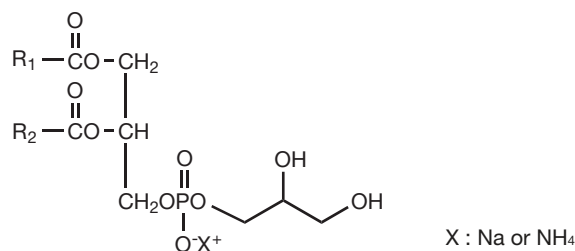
| | Product name | Description | PC purity | MW | R ₁ COO | R ₂ COO | Tc |
|---------------|--------------------|---|-----------|-------|--------------------|--------------------|-----|
| DDPC | COATSOME MC-1010 | 1,2-Didecanoyl-sn-glycero-3-phosphocholine | 99% up | 565.7 | C10:0 | C10:0 | -6 |
| DLPC | COATSOME MC-2020 | 1,2-Dilauroyl-sn-glycero-3-phosphocholine | 99% up | 621.8 | C12:0 | C12:0 | 0 |
| DMPC | COATSOME MC-4040 | 1,2-Dimyristoyl-sn-glycero-3-phosphocholine | 99% up | 677.9 | C14:0 | C14:0 | 23 |
| DPPC | COATSOME MC-6060 | 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine | 99% up | 734.0 | C16:0 | C16:0 | 41 |
| DSPC | COATSOME MC-8080 | 1,2-Distearoyl-sn-glycero-3-phosphocholine | 99% up | 790.2 | C18:0 | C18:0 | 55 |
| DOPC | COATSOME MC-8181 | 1,2-Dioleoyl-sn-glycero-3-phosphocholine | 99% up | 786.1 | C18:1 | C18:1 | -22 |
| DLoPC | COATSOME MC-8282 | 1,2-Dilinoleoyl-sn-glycero-3-phosphocholine | 99% up | 782.2 | C18:2 | C18:2 | -53 |
| DEPC | COATSOME MC-2121AL | 1,2-Dierucoyl-sn-glycero-3-phosphocholine | 99% up | 898.3 | C22:1 | C22:1 | -13 |
| EPA-PC | COATSOME MC-1515AL | 1,2-Dieicosapentaenoyl-sn-glycero-3-phosphocholine | 98% up | 826.2 | C20:5 | C20:5 | - |
| DHA-PC | COATSOME MC-2626AL | 1,2-Didocosahexaenoyl-sn-glycero-3-phosphocholine | 98% up | 878.2 | C22:6 | C22:6 | - |
| MPPC | COATSOME MC-4060 | 1-Myristoyl-2-palmitoyl-sn-glycero-3-phosphocholine | 99% up | 706.0 | C14:0 | C16:0 | 35 |
| MSPC | COATSOME MC-4080 | 1-Myristoyl-2-stearoyl-sn-glycero-3-phosphocholine | 99% up | 734.0 | C14:0 | C18:0 | 40 |
| PMPC | COATSOME MC-6040 | 1-Palmitoyl-2-myristoyl-sn-glycero-3-phosphocholine | 99% up | 706.0 | C16:0 | C14:0 | 28 |
| PSPC | COATSOME MC-6080 | 1-Palmitoyl-2-stearoyl-sn-glycero-3-phosphocholine | 99% up | 762.1 | C16:0 | C18:0 | 49 |
| SMPC | COATSOME MC-8040 | 1-Stearoyl-2-myristoyl-sn-glycero-3-phosphocholine | 99% up | 734.0 | C18:0 | C14:0 | 30 |
| SPPC | COATSOME MC-8060 | 1-Stearoyl-2-palmitoyl-sn-glycero-3-phosphocholine | 99% up | 762.1 | C18:0 | C16:0 | 44 |
| MOPC | COATSOME MC-4081 | 1-Myristoyl-2-oleoyl-sn-glycero-3-phosphocholine | 99% up | 732.0 | C14:0 | C18:1 | - |
| POPC | COATSOME MC-6081 | 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine | 99% up | 760.1 | C16:0 | C18:1 | -3 |
| SOPC | COATSOME MC-8081 | 1-Stearoyl-2-oleoyl-sn-glycero-3-phosphocholine | 99% up | 788.1 | C18:0 | C18:1 | 6 |

2-2. Lyso-Phosphatidylcholine



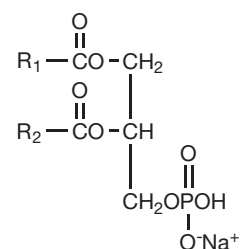
| | Product name | Description | PC purity | MW | R ₁ COO |
|-----------------|-----------------|--|-----------|-------|--------------------|
| M-LysoPC | COATSOME MC-40H | 1-Myristoyl-2-lyso-sn-glycero-3-phosphocholine | 99% up | 467.6 | C14:0 |
| P-LysoPC | COATSOME MC-60H | 1-Palmitoyl-2-lyso-sn-glycero-3-phosphocholine | 99% up | 495.6 | C16:0 |
| S-LysoPC | COATSOME MC-80H | 1-Stearoyl-2-lyso-sn-glycero-3-phosphocholine | 99% up | 523.7 | C18:0 |
| O-LysoPC | COATSOME MC-81H | 1-Oleoyl-2-lyso-sn-glycero-3-phosphocholine | 99% up | 521.7 | C18:1 |

2-3. Phosphatidylglycerol



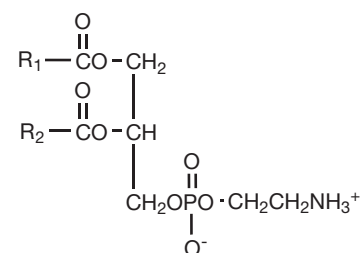
| | Product name | Description | PG purity | MW | R ₁ COO | R ₂ COO |
|----------------------------|--------------------|--|-----------|-------|--------------------|--------------------|
| HSPG-Na | COATSOME NG-21LS | Hydrogenated Soybean phosphatidylglycerol, sodium salt | 95% up | | | |
| EPG-Na | COATSOME NG-50LS | Non-hydrogenated Egg phosphatidylglycerol, sodium salt | 95% up | | | |
| DLPG-Na | COATSOME MG-2020LS | 1,2-Dilauroyl-sn-glycero-3-phosphoglycerol, sodium salt | 99% up | 632.8 | C12:0 | C12:0 |
| DMPG-Na | COATSOME MG-4040LS | 1,2-Dimyristoyl-sn-glycero-3-phosphoglycerol, sodium salt | 99% up | 688.9 | C14:0 | C14:0 |
| DMPG-NH₄ | COATSOME MG-4040LA | 1,2-Dimyristoyl-sn-glycero-3-phosphoglycerol, ammonium salt | 99% up | 683.9 | C14:0 | C14:0 |
| DPPG-Na | COATSOME MG-6060LS | 1,2-Dipalmitoyl-sn-glycero-3-phosphoglycerol, sodium salt | 99% up | 745.0 | C16:0 | C16:0 |
| DPPG-NH₄ | COATSOME MG-6060LA | 1,2-Dipalmitoyl-sn-glycero-3-phosphoglycerol, ammonium salt | 98% up | 740.0 | C16:0 | C16:0 |
| DSPG-Na | COATSOME MG-8080LS | 1,2-Distearoyl-sn-glycero-3-phosphoglycerol, sodium salt | 99% up | 801.1 | C18:0 | C18:0 |
| DSPG-NH₄ | COATSOME MG-8080LA | 1,2-Distearoyl-sn-glycero-3-phosphoglycerol, ammonium salt | 99% up | 796.1 | C18:0 | C18:0 |
| DOPG-Na | COATSOME MG-8181LS | 1,2-Dioleoyl-sn-glycero-3-phosphoglycerol, sodium salt | 98% up | 797.0 | C18:1 | C18:1 |
| DEPG-Na | COATSOME MG-2121LS | 1,2-Dierucoyl-sn-glycero-3-phosphoglycerol, sodium salt | 98% up | 909.2 | C22:1 | C22:1 |
| POPG-Na | COATSOME MG-6081LS | 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol, sodium salt | 98% up | 771.0 | C16:0 | C18:1 |

2-4. Phosphatidic acid



| | Product name | Description | PA purity | MW | R ₁ COO | R ₂ COO |
|----------------|--------------------|---|-----------|-------|--------------------|--------------------|
| DLPA-Na | COATSOME MA-2020LS | 1,2-Dilauroyl-sn-glycero-3-phosphatidic acid, sodium salt | 98% up | 558.7 | C12:0 | C12:0 |
| DMPA-Na | COATSOME MA-4040LS | 1,2-Dimyristoyl-sn-glycero-3-phosphatidic acid, sodium salt | 98% up | 614.8 | C14:0 | C14:0 |
| DPPA-Na | COATSOME MA-6060LS | 1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid, sodium salt | 99% up | 670.9 | C16:0 | C16:0 |
| DSPA-Na | COATSOME MA-8080LS | 1,2-Distearoyl-sn-glycero-3-phosphatidic acid, sodium salt | 99% up | 727.0 | C18:0 | C18:0 |

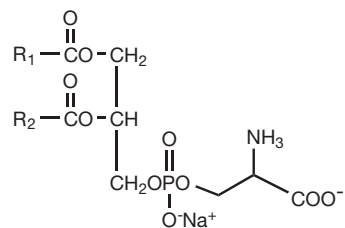
2-5. Phosphatidylethanolamine



| | Product name | Description | PE purity | MW | R ₁ COO | R ₂ COO |
|--------------|--------------------|---|-----------|-------|--------------------|--------------------|
| HSPE | COATSOME NE-21* | Hydrogenated Soybean phosphatidylethanolamine | 95% up | | | |
| EPE | COATSOME NE-50* | Non-hydrogenated Egg phosphatidylethanolamine | 95% up | | | |
| DLPE | COATSOME ME-2020 | 1,2-Dilauroyl-sn-glycero-3-phosphoethanolamine | 99% up | 579.8 | C12:0 | C12:0 |
| DMPE | COATSOME ME-4040 | 1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine | 99% up | 635.9 | C14:0 | C14:0 |
| DPPE | COATSOME ME-6060 | 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine | 99% up | 692.0 | C16:0 | C16:0 |
| DSPE | COATSOME ME-8080 | 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine | 99% up | 748.1 | C18:0 | C18:0 |
| DOPE | COATSOME ME-8181 | 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine | 99% up | 744.0 | C18:1 | C18:1 |
| DLoPE | COATSOME ME-8282 | 1,2-Dilinoleoyl-sn-glycero-3-phosphoethanolamine | 99% up | 740.0 | C18:2 | C18:2 |
| DEPE | COATSOME ME-2121AL | 1,2-Dierucoyl-sn-glycero-3-phosphoethanolamine | 99% up | 856.3 | C22:1 | C22:1 |
| POPE | COATSOME ME-6081 | 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine | 99% up | 718.0 | C16:0 | C18:1 |

* : make-to-order

2-6. Phosphatidylserine



| | Product name | Description | PS purity | MW | R ₁ COO | R ₂ COO |
|----------------|--------------------|--|-----------|-------|--------------------|--------------------|
| DMPS-Na | COATSOME MS-4040LS | 1,2-Dimyristoyl-sn-glycero-3-phospho-L-serine, sodium salt | 85% up | 701.8 | C14:0 | C14:0 |
| DPPS-Na | COATSOME MS-6060LS | 1,2-Dipalmitoyl-sn-glycero-3-phospho-L-serine, sodium salt | 85% up | 758.0 | C16:0 | C16:0 |
| DSPS-Na | COATSOME MS-8080LS | 1,2-Distearoyl-sn-glycero-3-phospho-L-serine, sodium salt | 85% up | 814.1 | C18:0 | C18:0 |
| DOPS-Na | COATSOME MS-8181LS | 1,2-Dioleoyl-sn-glycero-3-phospho-L-serine, sodium salt | 97% up | 810.0 | C18:1 | C18:1 |
| POPS-Na | COATSOME MS-6081LS | 1-Palmitoyl-2-oleoyl-sn-3-phospho-L-serine, sodium salt | 85% up | 784.0 | C16:0 | C18:1 |

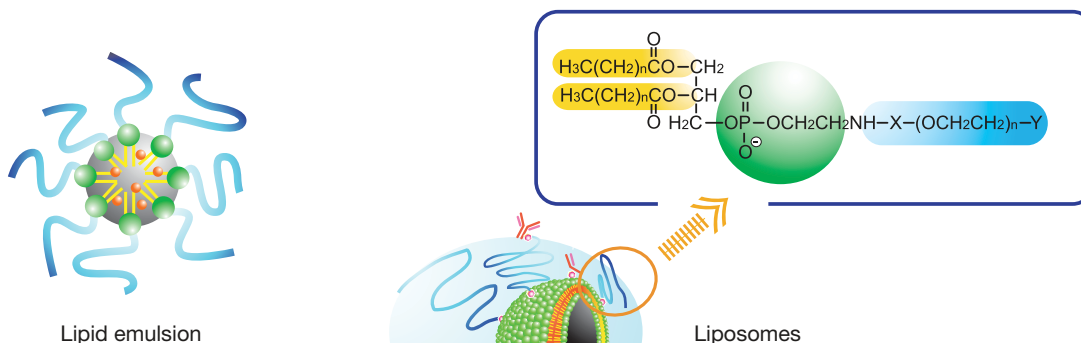
3. PEGylated Lipids

PEGylated lipids can be applied to liposomal drug formulations to prolong the circulating plasma half-life of drugs. Coating of the liposomal surface with polyethylene glycol suppresses drug clearance in vivo by the reticuloendothelial system, thereby prolonging the half-life of the drug.

PEG-modified lipids can also be used as emulsifiers and stabilizers of microspheres in aqueous solutions.

PEG 修飾脂質は、体内投与において血中滞留性を高める目的でリポソーム薬剤に用いることができます。ポリエチレングリコールでリポソーム表面を覆うことにより、細網内皮系への取り込みを抑え、血中での滞留時間を延長することができます。

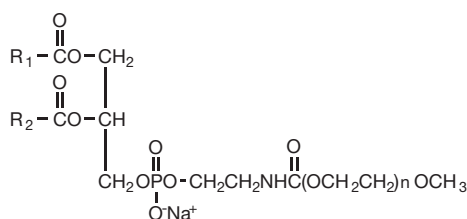
また、乳化剤および水溶液中での微粒子の安定剤としても使用することができます。



3-1. PEG-phospholipids

PEG-phospholipids of the carbamate-linked type are resistant to hydrolysis, and therefore used for commercial production of PEGylated liposomes. As NOF employs its own high-quality Activated PEGs and phospholipids, high-quality PEG-phospholipids can be supplied.

カーバメート結合タイプの PEG-リン脂質は、加水分解に対して安定であり、現在市販されている PEG-リポソームに用いられています。日油の高品質な活性化 PEG とリン脂質を原料として用いることにより、高品質な PEG-リン脂質を供給できます。

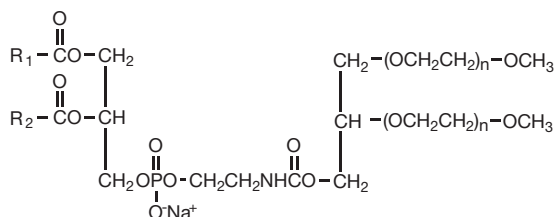


| Product name | Description | PEG MW | R1COO | R2COO |
|----------------------|---|--------|-------|-------|
| SUNBRIGHT DSPE-020CN | N-(Carbonyl-methoxypolyethyleneglycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 2,000 | C18:0 | C18:0 |
| SUNBRIGHT DSPE-050CN | N-(Carbonyl-methoxypolyethyleneglycol 5000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 5,000 | C18:0 | C18:0 |
| SUNBRIGHT PP-020CN* | N-(Carbonyl-methoxypolyethyleneglycol 2000)-1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 2,000 | C16:0 | C16:0 |
| SUNBRIGHT PP-050CN* | N-(Carbonyl-methoxypolyethyleneglycol 5000)-1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 5,000 | C16:0 | C16:0 |
| SUNBRIGHT PM-020CN* | N-(Carbonyl-methoxypolyethyleneglycol 2000)-1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 2,000 | C14:0 | C14:0 |

NOF CORPORATION is the sole patent holder of these high-quality PEG-phospholipids.

SUNBRIGHT® *: make-to-order

※ Patent No. : US6679822



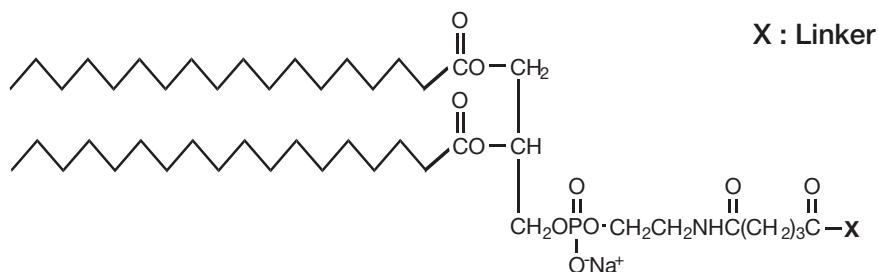
| Product name | Description | PEG MW | R1COO | R2COO |
|-------------------------|---|--------|-------|-------|
| SUNBRIGHT DSPE-020GL2U* | N-[Carbonyl-2',3'-Bis(methoxypolyethyleneglycol 2000)]-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 2,000 | C18:0 | C18:0 |
| SUNBRIGHT DSPE-050GL2U* | N-[Carbonyl-2',3'-Bis(methoxypolyethyleneglycol 5000)]-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt | 5,000 | C18:0 | C18:0 |

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3-2. New hydrophilic phospholipid derivatives

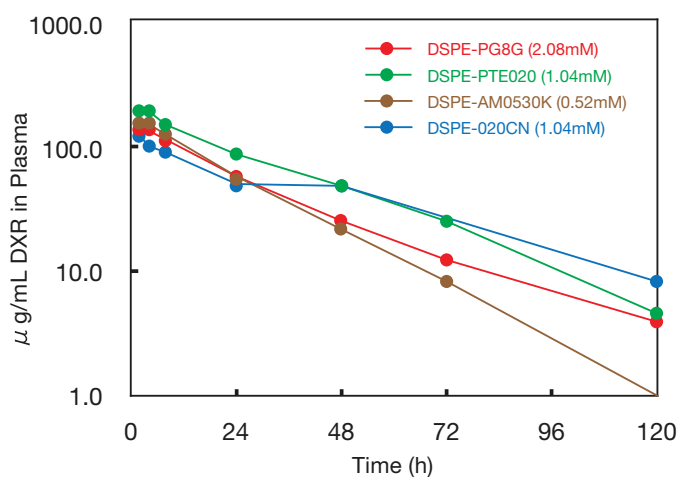
As listed below, NOF provides new types of phospholipid derivatives bound to polyglycerin and multi-arm PEGs as hydrophilic polymers.

次に示したように、水溶性ポリマーとしてポリグリセリンおよびマルチアーム PEG を付与した新しいタイプのリン脂質誘導体を供給します。



| | Product name | Polymer MW | Linker(X) |
|-----------------------------|----------------------------|------------|---|
| DSPE-Polyglycerin | SUNBRIGHT DSPE-PG8G* | 700 | $\left[\begin{array}{c} \text{CH}_2\text{OH} \\ \\ (\text{CH}_2\text{CHO}) \end{array} \right]_8 \text{H}$ |
| DSPE-Multi-arm PEG | SUNBRIGHT DSPE-PTE020* | 2,000 | |
| DSPE-Comb-shaped PEG | SUNBRIGHT DSPE-AM0530K* | 20,000 | $\left[\begin{array}{c} \text{CHCH}_2 \\ \\ \text{CH}_2 \\ \\ \text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_3 \end{array} \begin{array}{c} \text{CH} \\ \\ \text{O}=\text{C} \\ \\ \text{O} \end{array} \begin{array}{c} \text{CH} \\ \\ \text{C}=\text{O} \\ \\ \text{O} \end{array} \right]_k$ |

SUNBRIGHT® *: make-to-order

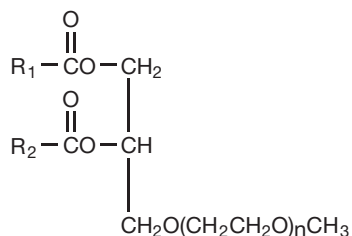


In vivo Plasma Clearance Profile for PEG-based Liposomes and Polyglycerine-based Liposome

3-3. Diacylglycerol-PEG

Because of direct attachment of PEG chains to diacylglycerol, this product series is devoid of phosphorylethanolamine groups and other coupling chemistry. Accordingly, they are resistant to hydrolysis and are suitable for application to drugs that are vulnerable to ionic charges.

Concerning this product, NOF has officially registered its product patent in Japan.



このシリーズは、ジアシルグリセロールに PEG 鎖を直接付与しており、フォスホリルエタノールアミン基およびその他の結合部位を含まないため、加水分解に対して安定であり、電荷が問題となる薬剤への使用に適しています。

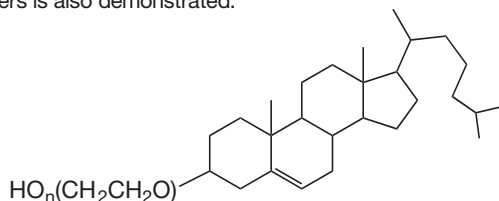
また、本製品に関しまして、日油の物質特許が日本で成立しています。

| Product name | Description | PEG MW | R ₁ COO | R ₂ COO |
|-------------------|---|--------|--------------------|--------------------|
| SUNBRIGHT GM-020 | 1,2-Dimyristoyl-sn-glycerol, methoxypolyethylene Glycol | 2,000 | C14:0 | C14:0 |
| SUNBRIGHT GM-050* | 1,2-Dimyristoyl-sn-glycerol, methoxypolyethylene Glycol | 5,000 | C14:0 | C14:0 |
| SUNBRIGHT GP-020 | 1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene Glycol | 2,000 | C16:0 | C16:0 |
| SUNBRIGHT GP-050* | 1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene Glycol | 5,000 | C16:0 | C16:0 |
| SUNBRIGHT GS-020 | 1,2-Distearoyl-sn-glycerol, methoxypolyethylene Glycol | 2,000 | C18:0 | C18:0 |
| SUNBRIGHT GS-050 | 1,2-Distearoyl-sn-glycerol, methoxypolyethylene Glycol | 5,000 | C18:0 | C18:0 |
| SUNBRIGHT GO-020 | 1,2-Dioleoyl-sn-glycerol, methoxypolyethylene Glycol | 2,000 | C18:1 | C18:1 |
| SUNBRIGHT GO-050* | 1,2-Dioleoyl-sn-glycerol, methoxypolyethylene Glycol | 5,000 | C18:1 | C18:1 |

SUNBRIGHT® * : make-to-order

3-4. Cholesterol-PEG derivatives

In addition to methoxypolyethyleneglycol, NOF provides various kinds of high-purity monoalkyl-substituted polyethyleneglycols. When hydrocarbon moieties comprising more than 8 carbons in the alkyl groups are used, several unique surface-active effects can be obtained. These derivatives can be employed not only for surface modification of liposomes, but also for PEGylation of proteins by the introduction of various functional groups to the PEG chain terminals. Usefulness of these products as solubilizers is also demonstrated.

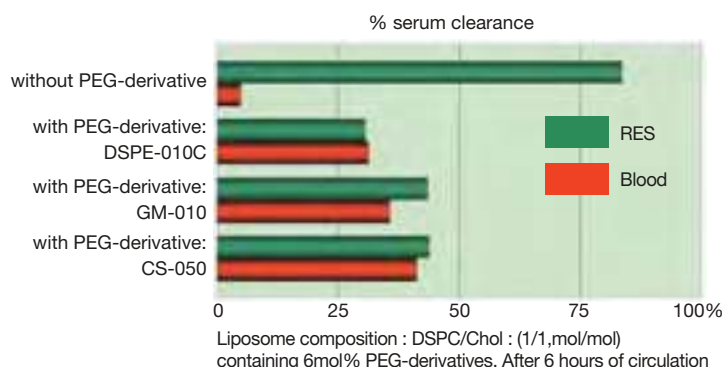


メトキシポリエチレングリコール以外にも、さまざまな種類の高純度モノアルキル置換ポリエチレングリコールを開発しています。アルキル基として炭素数が 8 以上の炭化水素基を用いると、種々の界面活性効果が出てきます。これらの誘導体はそのままリポソームなどの表面修飾に用いることができるのみではなく、末端に種々の官能基を導入してたん白質などの PEG 化にも使うことができます。また、可溶化剤として有用な効果も認められています。

| Product name | Description | Total MW | Average PEG Unit |
|------------------|--|----------|------------------|
| SUNBRIGHT CS-010 | Poly(oxy-1,2-ethanediyl), .alpha.-(3.beta.)-cholest-5-en-3-yl-.omega.-hydroxy- | 1,000 | 14 |
| SUNBRIGHT CS-020 | Poly(oxy-1,2-ethanediyl), .alpha.-(3.beta.)-cholest-5-en-3-yl-.omega.-hydroxy- | 2,000 | 37 |
| SUNBRIGHT CS-050 | Poly(oxy-1,2-ethanediyl), .alpha.-(3.beta.)-cholest-5-en-3-yl-.omega.-hydroxy- | 5,000 | 105 |

SUNBRIGHT®

Serum clearance efficiency of new PEG-Lipid derivatives in Liposomes

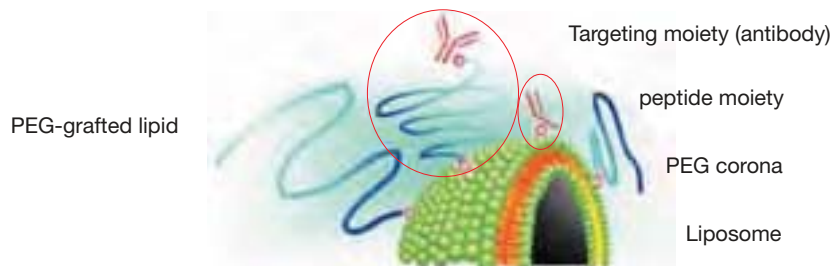


References: K. Maruyama et al., *Bio. Pharm. Bull.* **19(10)**, 1347 (1996)

4. Functionalized Phospholipids

Use of functionalized phospholipids enables researchers to do protein lipidation, attaching various peptides or other biologics to the surfaces of lipid emulsions or liposomes that allows some desired target features to be obtained, and increase of the plasma half-life of the modified drugs with the introduction of PEG chains into the target drugs. NOF can supply various kinds of high-purity derivatives because we have the advantage of manufacturing our own pure, highly reactive PEG.

機能性リン脂質を用いると、蛋白質の脂質修飾や脂肪乳剤やリポソームの表面に種々のペプチドや抗体などを結合させ target 性を付与したり、PEG 鎖を導入して処方血中の滞留性をあげることができます。当社は原料 PEG から合成しておりますので、高純度な種々の誘導体を提供いたします。

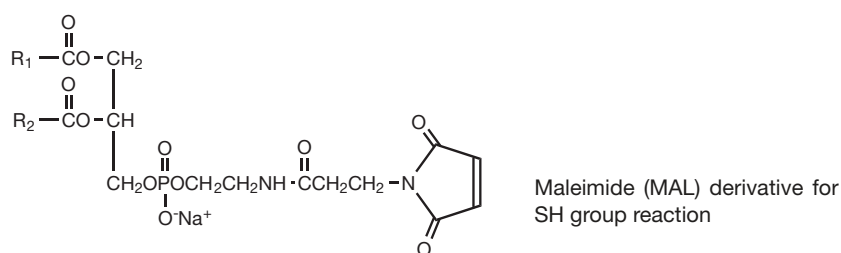


4-1. Activated phospholipids

Activated phospholipids include both maleimide groups reactive with -SH groups in biologics, and activated carboxylic esters which react with -NH₂ and -SH groups in proteins.

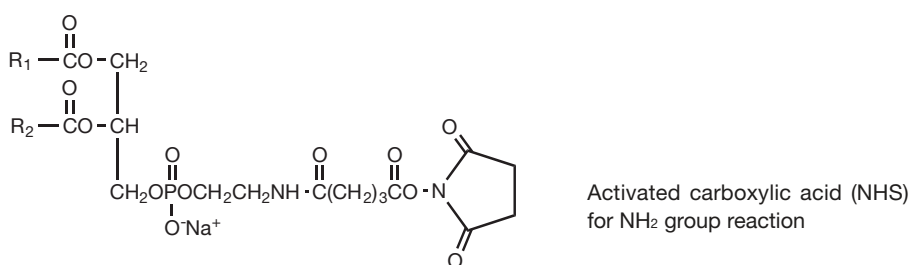
活性化リン脂質には、抗体などの SH 基と反応するマレイミド基を持つタイプと、蛋白質などの NH₂ 基や SH 基と反応する活性化カルボキシル基を持つタイプがあります。

MAL-Phospholipid



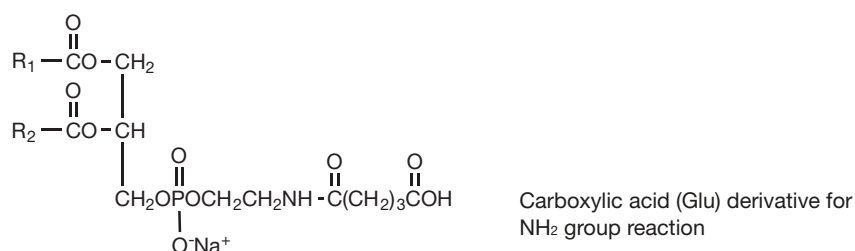
| | Product name | Description | R ₁ C00 | R ₂ C00 | MW |
|----------|---------------------|--|--------------------|--------------------|-------|
| DMPE-MAL | COATSOME FE-4040MA3 | N-(3-Maleimide-1-oxopropyl)-L-α-phosphatidylethanolamine, Dimyristoyl | C14:0 | C14:0 | 809.0 |
| DPPE-MAL | COATSOME FE-6060MA3 | N-(3-Maleimide-1-oxopropyl)-L-α-phosphatidylethanolamine, Dipalmitoyl | C16:0 | C16:0 | 865.1 |
| DSPE-MAL | COATSOME FE-8080MA3 | N-(3-Maleimide-1-oxopropyl)-L-α-phosphatidylethanolamine, Distearoyl | C18:0 | C18:0 | 921.2 |
| POPE-MAL | COATSOME FE-6081MA3 | N-(3-Maleimide-1-oxopropyl)-L-α-phosphatidylethanolamine, 1-Palmitoyl-2-oleoyl | C16:0 | C18:1 | 891.1 |
| DOPE-MAL | COATSOME FE-8181MA3 | N-(3-Maleimide-1-oxopropyl)-L-α-phosphatidylethanolamine, Dioleoyl | C18:1 | C18:1 | 917.1 |

NHS-Phospholipid

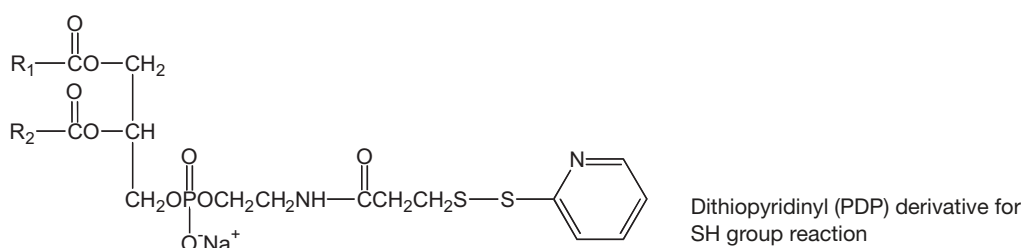


| | Product name | Description | R ₁ C00 | R ₂ C00 | MW |
|----------|---------------------|--|--------------------|--------------------|-------|
| DMPE-NHS | COATSOME FE-4040SU5 | N-(Succinimidyl-oxy-glutaryl)-L-α-phosphatidylethanolamine, Dimyristoyl | C14:0 | C14:0 | 869.0 |
| DPPE-NHS | COATSOME FE-6060SU5 | N-(Succinimidyl-oxy-glutaryl)-L-α-phosphatidylethanolamine, Dipalmitoyl | C16:0 | C16:0 | 925.1 |
| DSPE-NHS | COATSOME FE-8080SU5 | N-(Succinimidyl-oxy-glutaryl)-L-α-phosphatidylethanolamine, Distearoyl | C18:0 | C18:0 | 981.2 |
| POPE-NHS | COATSOME FE-6081SU5 | N-(Succinimidyl-oxy-glutaryl)-L-α-phosphatidylethanolamine, 1-Palmitoyl-2-oleoyl | C16:0 | C18:1 | 951.2 |
| DOPE-NHS | COATSOME FE-8181SU5 | N-(Succinimidyl-oxy-glutaryl)-L-α-phosphatidylethanolamine, Dioleoyl | C18:1 | C18:1 | 977.2 |

Glu-Phospholipid

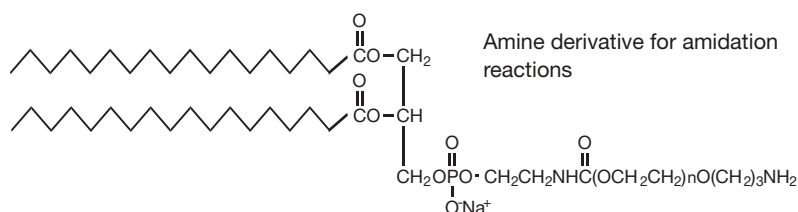


| | Product name | Description | R ₁ COO | R ₂ COO | MW |
|----------|--------------------|---|--------------------|--------------------|-------|
| DMPE-Glu | COATSOME FE-4040GL | N-Glutaryl-L-α-phosphatidylethanolamine, Dimyristoyl | C14:0 | C14:0 | 771.9 |
| DPPE-Glu | COATSOME FE-6060GL | N-Glutaryl-L-α-phosphatidylethanolamine, Dipalmitoyl | C16:0 | C16:0 | 828.1 |
| DSPE-Glu | COATSOME FE-8080GL | N-Glutaryl-L-α-phosphatidylethanolamine, Distearoyl | C18:0 | C18:0 | 884.2 |
| POPE-Glu | COATSOME FE-6081GL | N-Glutaryl-L-α-phosphatidylethanolamine, 1-Palmitoyl-2-oleoyl | C16:0 | C18:1 | 854.1 |
| DOPE-Glu | COATSOME FE-8181GL | N-Glutaryl-L-α-phosphatidylethanolamine, Dioleoyl | C18:1 | C18:1 | 880.1 |

PDP-Phospholipid **New**

| | Product name | Description | R ₁ COO | R ₂ COO | MW |
|----------|--------------------|---|--------------------|--------------------|------------------|
| DPPE-PDP | COATSOME FE-6060DT | N-[3-(2-Pyridinyldithio)-1-oxopropyl]-L-α-phosphatidylethanolamine, Dipalmitoyl | C16:0 | C16:0 | 911.2 New |

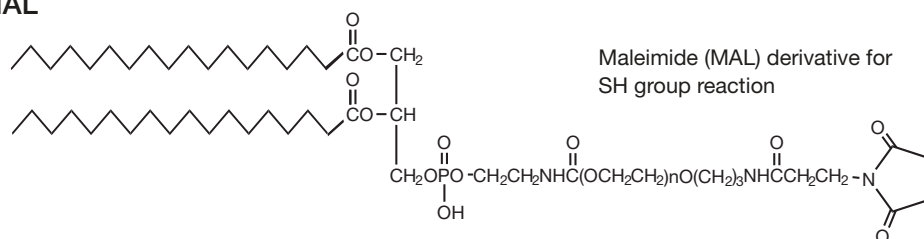
4-2. Activated PEG phospholipids

Phospholipid-PEG-NH₂

| | Product name | Description | PEG MW |
|--------------------------|-----------------------|---|--------|
| DSPE-PEG-NH ₂ | SUNBRIGHT DSPE-020PA | N-(aminopropyl polyethyleneglycol)carbamyl- distearoylphosphatidyl-ethanolamine | 2,000 |
| DSPE-PEG-NH ₂ | SUNBRIGHT DSPE-034PA* | N-(aminopropyl polyethyleneglycol)carbamyl- distearoylphosphatidyl-ethanolamine | 3,400 |
| DSPE-PEG-NH ₂ | SUNBRIGHT DSPE-050PA | N-(aminopropyl polyethyleneglycol)carbamyl- distearoylphosphatidyl-ethanolamine | 5,000 |

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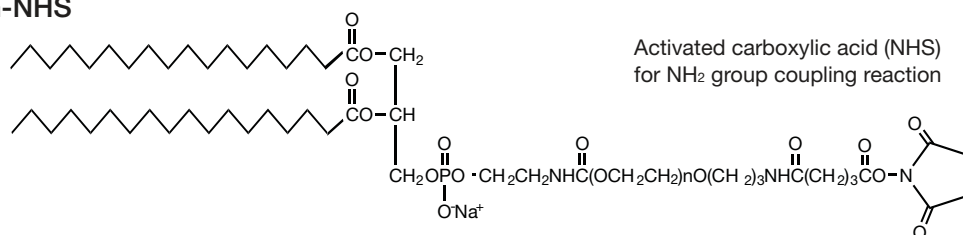
Phospholipid-PEG-MAL



| | Product name | Description | PEG MW |
|--------------|-----------------------|--|--------|
| DSPE-PEG-MAL | SUNBRIGHT DSPE-020MA | N-[(3-Maleimide-1-oxopropyl)aminopropyl polyethyleneglycol-carbamyl] distearoylphosphatidyl-ethanolamine | 2,000 |
| DSPE-PEG-MAL | SUNBRIGHT DSPE-034MA | N-[(3-Maleimide-1-oxopropyl)aminopropyl polyethyleneglycol-carbamyl] distearoylphosphatidyl-ethanolamine | 3,400 |
| DSPE-PEG-MAL | SUNBRIGHT DSPE-050MA* | N-[(3-Maleimide-1-oxopropyl)aminopropyl polyethyleneglycol-carbamyl] distearoylphosphatidyl-ethanolamine | 5,000 |

SUNBRIGHT® * : make-to-order

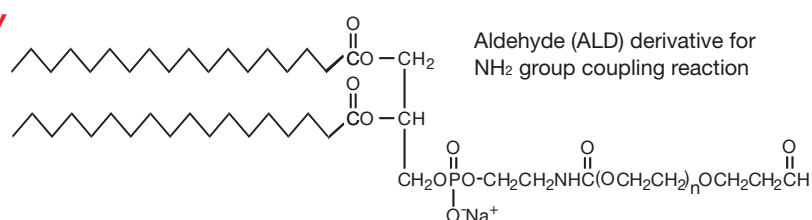
Phospholipid-PEG-NHS



| Product name | Description | PEG MW |
|---------------------|-----------------------|--------|
| DSPE-PEG-NHS | SUNBRIGHT DSPE-020GS | 2,000 |
| DSPE-PEG-NHS | SUNBRIGHT DSPE-034GS* | 3,400 |
| DSPE-PEG-NHS | SUNBRIGHT DSPE-050GS* | 5,000 |

SUNBRIGHT® *: make-to-order

Phospholipid-PEG-ALD New

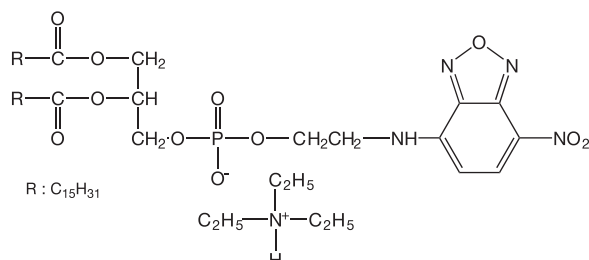


| Product name | Description | PEG MW |
|---------------------|-----------------------|--------|
| DSPE-PEG-ALD | SUNBRIGHT DSPE-034AL* | 3,400 |

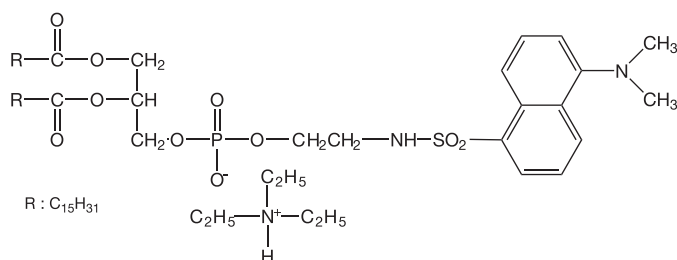
SUNBRIGHT® *: make-to-order

4-3. Fluorescent phospholipids

NBD-DPPE

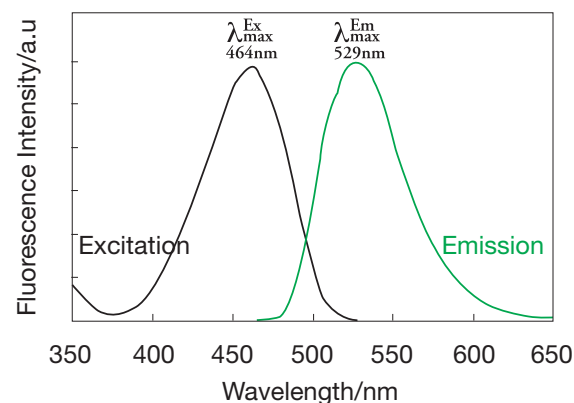


Dansyl-DPPE

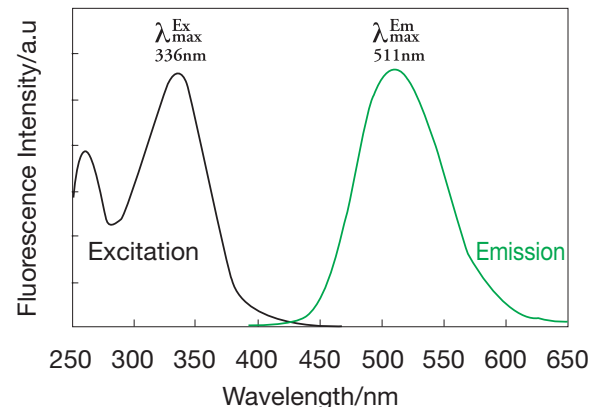


| Product name | Description | MW | R ₁ COO | R ₂ COO |
|--------------------|--------------------|--------|--------------------|--------------------|
| NBD-DPPE | COATSOME FE-6060NB | 956.3 | C16:0 | C16:0 |
| Dansyl-DPPE | COATSOME FE-6060DA | 1026.5 | C16:0 | C16:0 |

NBD-DPPE

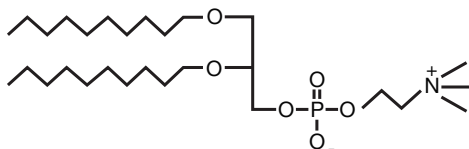


Dansyl-DPPE



5. Novel Lipids and Cationic Lipids

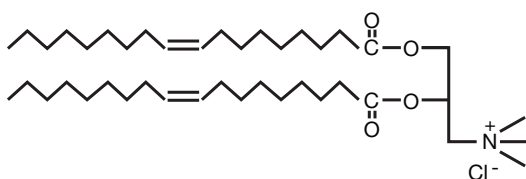
5-1. Ether phospholipid



| Product name | Description | MW |
|------------------|------------------|--|
| C10:0 Diether PC | COATSOME EC-1010 | 1,2-Di-O-Decyl-sn-glycero-3-phosphocholine |
| | | 537.8 |

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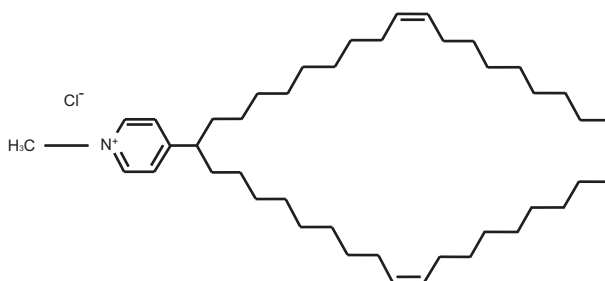
5-2. DOTAP



| Product name | Description | MW |
|--------------|--------------------|--|
| DOTAP | COATSOME CL-8181TA | 1,2-Dioleoyloxy-3-trimethylammonium propane chloride |
| | | 698.5 |

COATSOME®

5-3. SAINT™-Solid-1(SN-010) New



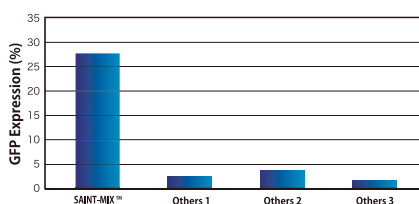
| Product name | Description | MW |
|------------------------|--|-------|
| SAINT™-Solid-1(SN-010) | 4-[(9Z,28Z)-heptatriaconta-9,28-dien-19-yl]-1-methylpyridin-1-ium chloride | 644.5 |

New

Patent No. :EP755924, US5853694, US6726894. Licensing information is available from Synvolux Therapeutics B.V.

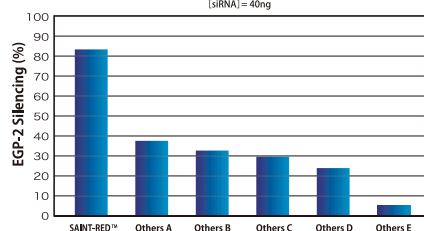
DNA Delivery

Comparison of GFP Expression in Murine Embryonic Stem Cells



siRNA Delivery

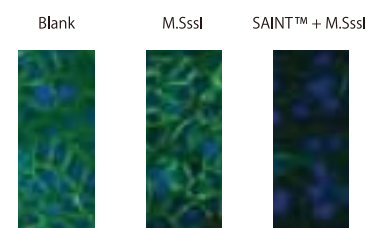
SAINT-RED™ Comparison
Silencing of EGP-2 in SKOV-3 Cells
[siRNA] = 40ng



Protein Delivery

Delivery of DNA Modifying Enzymes

Delivery of DNA methyltransferase M.Sss I into high E-cadherin expressing T6HBE cells



References :

- Bernardia T.F. van der Gun, et al., *J Control Release* **123**, 228-238 (2007)
 Bernardia T.F. van der Gun, et al., *Int. J. Cancer* **123**, 484-489 (2008)
 Sigridur A. Asgeisdottir, et al., *J Control Release* **141**, 241-251 (2010)
 Joanna E. Adrian, et al., *J Control Release* **144**, 341-349 (2007)

Note :

This product is covered by one or more patent applications and/or foreign counter-part patent applications owned by Synvolux Therapeutics B.V.

6. Empty Liposomes <COATSOME® EL Series>



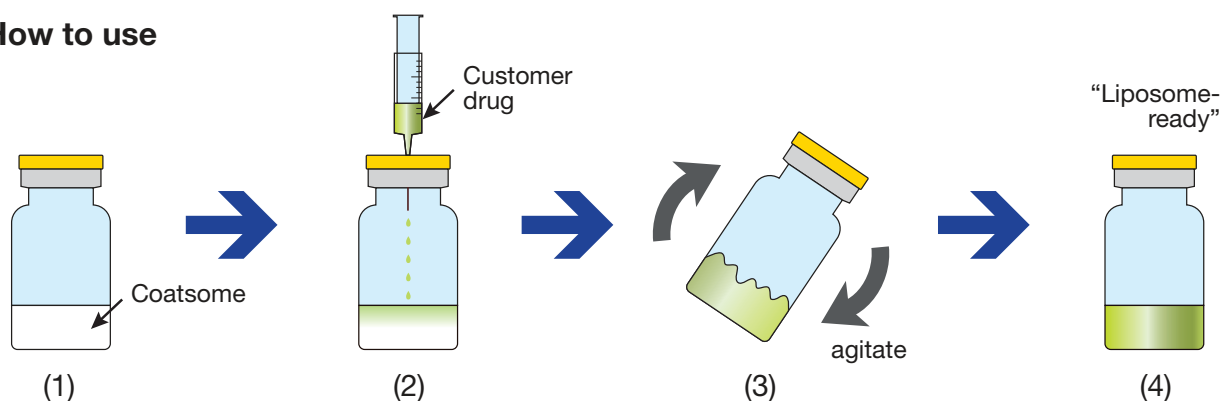
In general, preparation of liposomal drugs requires tedious adjustments of the liposomal composition and also control of the particle size and encapsulation efficiency, which make researchers usually reluctant to formulate liposomal drugs. NOF has successfully overcome these problems by developing unique experimental kits for the investigation of liposomal drug delivery systems (DDS).

Freeze-dried ready-to-use liposome powder, called Empty Liposomes, filled in vials is composed of several kinds of phospholipids and electrolytes. When a drug solution is injected into a vial and gently shaken, the drug is easily encapsulated in the liposomes. Empty Liposomes have a special advantage in that even drugs such as the anthracyclines and aminoglycosides can be efficiently encapsulated without the need for special technologies such as extrusion.

一般に、リポソーム化医薬品を作製するためには、リン脂質組成、粒径調整、内包化率などの調整が必要であり、研究者にとってリポソーム化医薬品が容易に処方できない原因となっていました。当社はこれらの問題を解決すべくリポソーム型 DDS 検用キットにユニークな研究用キットを開発しました。

中空リポソームと称するバイアルに入った凍結乾燥リポソーム粉末は、数種類のリン脂質と電荷物質で構成されていて、医薬品を溶解させた溶液をバイアルに注入し緩やかに混和することにより、簡単に医薬品をリポソーム中に内包させることができます。中空リポソームを用いることによりエクストルージョン等の特殊な技術を用いることなく、特にアントラサイクリンやアミノグルコシドなどの医薬品を高収率で容易に内包できます。

How to use



- (1) COATSOME EL removed from cool storage and allowed to come to room temperature.
- (2) Add aqueous solution of a drug in the temperature range of 16°C to 40°C.
- (3) Shake the vial gently three to five times by hand.
- (4) The liposomal drug is now ready for use.

- (1) COATSOME EL を冷蔵庫から取り出し、室温に達するまで放置します。
- (2) 温度 16℃から 40℃の範囲内で、薬物水溶液を注入します。
- (3) バイアルを手を持ち、3 回から 5 回振ります。
- (4) リポソーム化医薬品の出来上がり。

6-1. EL Series Product Characteristics

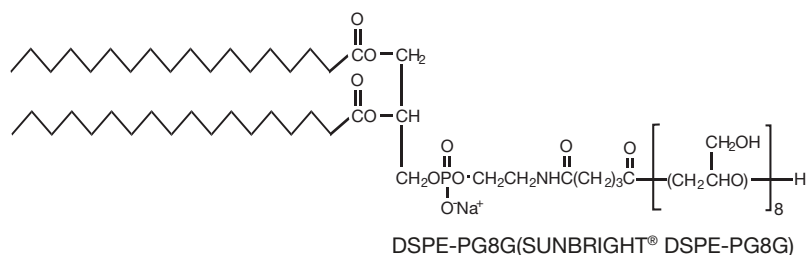
Product compositions and characteristics are shown below. Cationic charged liposomes are prepared by incorporating stearylamine as a charged lipid into the formulation. Nonionic and anionic charged liposomes are prepared by altering the ratio of DPPG as the charged lipid. While preparing an aqueous solution of the drug in water (Distilled Water for Injection), it is necessary to decide the concentrations according to the molarity of the DPPG as the charged lipid. For further details, please refer to "Suggestions for use" in the next section.

製品の組成と特性を以下に示します。カチオン性リポソームは電荷脂質であるステアリンアミンを処方に入れて作製しています。ノニオン性リポソームとアニオン性リポソームは、電荷脂質である DPPG のモル数を変化させて作製しています。薬物を水（注射用蒸留水）に溶解させて薬物水溶液を作製する際には、電荷脂質のモル数に応じて濃度を決める必要があります。詳細は次項の作製法をご覧ください。

•COATSOME® EL Series

| Product Name | Charge | Lipid Composition($\mu\text{mol/vial}$) | Total amount of lipids(mg) |
|------------------|----------------------------|---|----------------------------|
| COATSOME EL-01-C | Cationic | DPPC:Cholesterol:Stearyl amine=52:40:8 | 57 |
| COATSOME EL-01-N | Nonionic | DPPC:Cholesterol:DPPG=54:40:6 | 61 |
| COATSOME EL-01-A | Anionic | DPPC:Cholesterol:DPPG=30:40:30 | 61 |
| COATSOME EL-11-C | Cationic | POPC:Cholesterol:Stearyl amine=52:40:8 | 57 |
| COATSOME EL-11-N | Nonionic(Slightly anionic) | POPC:Cholesterol:POPG=54:40:6 | 61 |
| COATSOME EL-11-A | Anionic | POPC:Cholesterol:POPG=30:40:30 | 61 |

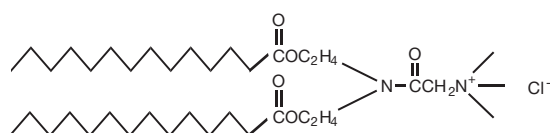
•COATSOME® EL-P Series



| Product Name | Charge | Lipid Composition($\mu\text{mol/vial}$) | Total amount of lipids(mg) |
|-------------------|------------------|--|----------------------------|
| COATSOME EL-01-PN | Slightly anionic | DSPE-PG8G:DPPC:Cholesterol:DPPG=4.2 : 20.5 : 15.2 : 2.3 | 29 |
| COATSOME EL-01-PA | Anionic | DSPE-PG8G:DPPC:Cholesterol:DPPG=4.2 : 11.4 : 15.2 : 11.4 | 29 |

•COATSOME® EL-01-D

We also provide new cationic liposomes (COATSOME EL-01-D) applicable to gene delivery systems. This novel cationic liposome contains not only O, O'-ditetradecanoyl-N-(α -trimethylammonioacetyl) diethanolamine chloride (DC-6-14) as a cationic lipid, but also DOPE and cholesterol, and confers the characteristics of efficient transfection activity and expression ability both in vitro serum-containing media and in vivo assay systems.



O,O'-ditetradecanoyl- N-(α -trimethylammonioacetyl)diethanolamine chloride (DC-6-14)

| Product Name | Lipid Composition($\mu\text{mol/vial}$) | Total amount of lipids(mg) |
|------------------|---|----------------------------|
| COATSOME EL-01-D | DOPE:Cholesterol:DC-6-14=0.75 : 0.75 : 1.00 | 1.51 |

また、遺伝子デリバリー用として新しいカチオニックリポソーム <COATSOME EL-01-D> を開発しました。COATSOME EL-01-D は、カチオン性脂質である O,O' -ditetradecanoyl-N-(α -trimethylammonioacetyl)diethanolamine chloride (DC-6-14) に加え、DOPE とコレステロールを含有し、in vitro の血清添加培地中や in vivo アッセイ系においても高い遺伝子導入・発現活性を有している新規なカチオン性リポソームです。

6-2. Suggestions for use

COATSOME® EL

How to use

- When 2 mL of distilled water is added, the osmotic pressure ratio of the product becomes 0.8 to 1.1. The osmotic pressure should be adjusted according to the need in the intended experiment.
- For enhancement of the encapsulation efficiency of the drug by electrostatic interaction, the molar ratio of the charged lipids (either stearylamine or DPPG) against the drug solution plays an important role; the molar ratio should be at least more than 2, and preferably not less than 3.
- Adjust the temperature range for storage of the aqueous drug solution between 16°C and 40°C.
- Use the liposomal drugs immediately after the adjustment. (Note: Not for use in humans.)

使用方法

- 2ml の蒸留水を添加することにより浸透圧が 0.8-1.1 となるように調整してあります。目的の実験によっては浸透圧の調整が必要です。
- 電氣的相互作用により内包率を向上させるためには、電荷脂質（ステアリルアミン、DPPG のいずれかが該当）の医薬品溶液に対するモル比が重要であり、そのモル比は 2 以上で好ましくは 3 以上です。
- 医薬品の水溶液は 16℃ から 40℃ の範囲に調整しておきます。
- 調整したリポソーム化医薬品は直ちにご使用ください。（人には使用できません）

6-3. Determination of liposome encapsulation efficiency

Method for removal of the unencapsulated drugs

(a) Dialysis

Place the prepared drug liposome solution in a dialyzing tube and dialyze it against an isotonic solution: the unencapsulated drug leaks into the isotonic solution outside the tube.

(b) Gel filtration

Pass the prepared liposome solution through a column filled with a packing material for gel filtration. The liposomes and the unencapsulated drug are eluted from the column in that order. Select the packing materials according to the molecular weight of the drug to be removed (e.g., Sephadex G-50 for low molecular weight, Sepharose 4B for high molecular weight).

(c) Centrifugation

When centrifugation is performed at high speeds after the addition of physiological saline (150mM NaCl), the liposomal drug is precipitated. After removal of the supernatant, add saline once again. This procedure usually needs to be repeated two or three times at 100,000rpm. Regardless of the procedure employed, it is absolutely essential to maintain both the inside and outside layers of the liposomes isotonic, and the temperature below the liposome phase transition temperature throughout the procedure. During centrifugation, the temperature should be below 40°C.

内包化率の測定

未内包化医薬品の除去による方法

(a) 透析

調整したリポソーム液は透析チューブに入れて、等張液により透析します。未内包化医薬品は等張液中に漏出します。

(b) ゲルろ過

調整したリポソーム液は、ゲルろ過用充填剤を入れたカラム中を通過させます。リポソームが先に、未内包化医薬品が後からカラムを通過して出てきます。医薬品の分子量によって、充填剤の種類 (例: Sephadex G-50: 低分子用、Sepharose 4B: 高分子用) を選択します。

(c) 遠心分離

生理食塩水 (150mM NaCl) を加えて高速度下で遠心分離を行うと、リポソーム化医薬品は沈んで得られます。上澄みを除去した後再度生理食塩水を加え、通常は 100,000 回転で 2 回から 3 回繰り返します。

これらのどの方法においても、リポソームの内層と外層を等張に維持することが必須であり、調整工程を通じて温度はリン脂質の相転移温度以下に保たなければなりません。この場合は 40°C 以下で行います。

Quantitative determination of the encapsulated drug

After removal of the non-encapsulated drug according to the methods described above, perform quantitative determination of the drug encapsulated in the liposomes after destroying the liposomes. Two methods are available for the destruction of liposomes; addition of surfactants and separation of the aqueous layer from the solvent layer by the addition of an appropriate solvent (chloroform). After decapsulating the liposomes, you can analyze the quantitative assay of the released drug by its own method.

内包化率の測定

上述したいずれかの方法で未内包化医薬品を除去した後、リポソームを破壊する方法によってリポソーム中に内包された医薬品の定量を行います。リポソームを破壊するには、界面活性剤を添加する方法と溶剤 (クロロホルム) を入れて水相と溶剤相とに分層する方法があります。いずれにしても、リポソームを破壊した後は、通常の方法にて医薬品の定量を行います。

6-4. Application Data for the COATSOME® EL Series

Cationic Liposomes, COATSOME® EL-01-C

| Drug | Particle Size (nm) | Encapsulation Efficiency (%) |
|-------------------------------|--------------------|------------------------------|
| Bucladesine sodium (0.5mg/ml) | 173 | 20-25 |
| Sodium salicylate (0.16mg/ml) | 162 | 40-45 |
| DNA (Salmon Testes, 100ug/ml) | 942 | 100 |

Nonionic Liposomes, COATSOME® EL-01-N

For enhancement of the encapsulation efficiency, the concentration of the cationic drug needs to be controlled at below 1mM. Thus, to achieve higher encapsulation efficiency, the molar ratio of DPPG (3mM) against the drug should be not less than 3.

内包効率を向上させるためには、カチオン性医薬品の濃度は 1mM 以下とする必要があります。高い内包効率を得るためには、DPPG (3mM) と医薬品とのモル比は 3 以上とする必要があります。

Anionic Liposomes, COATSOME® EL-01-A

| Drug | Particle Size (nm) | Encapsulation Efficiency (%) |
|-------------------------------------|--------------------|------------------------------|
| Doxorubicin hydrochloride (1mg/ml) | 150 | 97-100 |
| Amikacin sulfate (1mg/ml) | 140 | 98-100 |
| Streptomycin sulfate (1mg/ml) | 145 | 95-100 |
| Procainamide hydrochloride (1mg/ml) | 152 | 80-85 |
| Epirubicin hydrochloride (1mg/ml) | 146 | 97-100 |
| Pirarubicin hydrochloride (1mg/ml) | 129 | 97-100 |

Improvement of the encapsulation efficiency requires maintenance of the cationic drug concentration below 5mM. If higher encapsulation efficiency is desired, the molar ratio of DPPG (15mM) against the drug should be kept at not less than 3.

内包効率を向上させるためには、カチオン性医薬品の濃度は 5mM 以下とする必要があります。高い内包効率を得るためには、DPPG (15mM) と医薬品とのモル比は 3 以上とする必要があります。

Comparison of pharmacokinetics in vivo*

| Drug Maker | Liposome | AUC(%dose/ml-min) | MRT(min) | CL tot(ml/min/Kg) |
|------------|----------------|-------------------|----------|-------------------|
| Mannitol | EL Series | 237 | 448 | 0.174 |
| Mannitol | Bangham Method | 2204 | 398 | 0.179 |
| Inulin | EL Series | 2137 | 408 | 0.175 |
| Inulin | Bangham Method | 2315 | 373 | 0.174 |

*K.Yachi et al, *Biopharm. & Drug Dispos.* **17**, 589-605(1996):Composition:DPPC:DPPG:Chol=27:53:20 (Anionic Liposomes)

Cationic Liposomes for gene delivery (COATSOME® EL-01-D)

Transfection Activities *in vitro**¹ by Luciferase Assay*⁵ (Light units/mg protein · sec)

| | HRA | MEIL | ES-2 |
|-----------|--------|-------|-------|
| Serum (-) | 6,048 | 6,291 | 1,325 |
| Serum (+) | 11,378 | 2,913 | 689 |

Transfection Activities *in vivo**² in intraperitoneal disseminated tumors*⁵

| | Percentage of LacZ-positive cells | n |
|--------------------------|-----------------------------------|---|
| COATSOME EL-01-D | 1.00 ± 0.11 | 5 |
| Commercially available A | 0.38 ± 0.26 | 3 |
| Commercially available B | 0.62 ± 0.21 | 3 |
| Commercially available C | 0.23 ± 0.23 | 3 |

Relationship Between Transfection Efficiencies and Cell Mitotic Activities*³,*⁵

| Cell lines | Percentage of LacZ-positive cells | | Labeling index (%) |
|-------------------|-----------------------------------|--------------------------|--------------------|
| | COATSOME EL-01-D | Commercially available C | |
| Cancer cell lines | | | |
| HRA | 42.9 ± 3.8 | 4.7 ± 1.0 | 68.2 ± 1.6 |
| mEiIL | 4.5 ± 1.0 | 0.6 ± 0.1 | 41.0 ± 1.2 |
| ES-2 | 23.7 ± 1.9 | 3.3 ± 0.9 | 41.9 ± 4.5 |
| OVHS-1 | 0.8 ± 0.4 | 0.9 ± 0.3 | 6.1 ± 1.4 |
| MCAS | 1.3 ± 0.1 | < 0.1 | 51.5 ± 6.1 |
| SKOV3 | 11.6 ± 1.8 | 0.2 ± 0.2 | 35.2 ± 6.7 |
| OVCAR3 | 12.3 ± 1.1 | 0.4 ± 0.4 | 34.4 ± 3.7 |
| KK 2.7 ± | 2.7 ± 0.7 | 0.1 ± 0.1 | 26.2 ± 4.3 |
| KOC-3S | 5.9 ± 2.1 | 2.6 ± 1.6 | ND* ⁴ |
| Nakajima | 4.9 ± 1.7 | 0.1 ± 0.1 | ND* ⁴ |
| KF | 15.5 ± 2.3 | 0.1 ± 0.1 | ND* ⁴ |
| SW626 | 26.8 ± 4.6 | 0.2 ± 0.1 | ND* ⁴ |
| Colo320DM | 32.3 ± 3.2 | 5.2 ± 1.1 | ND* ⁴ |
| HRA | 42.9 ± 3.8 | 4.7 ± 1.0 | ND* ⁴ |
| mEiIL | 4.5 ± 1.0 | 0.6 ± 0.1 | ND* ⁴ |
| Normal cell lines | | | |
| Fibroblast (TIG) | 9.6 ± 2.2 | 0.9 ± 0.2 | 42.4 ± 10.7 |
| Fibroblast (IMR) | 2.5 ± 0.4 | 1.6 ± 0.5 | 14.2 ± 3.2 |
| HUVEC0103 | < 0.1 | < 0.1 | 22.2 ± 1.6 |
| HUVEC1204 | < 0.1 | 0.2 ± 0.1 | 11.3 ± 0.2 |
| HUVEC0923 | < 0.1 | < 0.1 | 18.2 ± 4.1 |

*1)Transfection performed in the absence or presence of 10% fetal bovine serum (FBS). Data shown represent mean of three experiments.

*2)mEIL cells growing in peritoneal cavities of nude mice were transfected with liposome/CAG-lacZ (20μg) and the percentage of lacZ-positive cells was determined. Data shown represent mean: ± SD.

*3)Percentages of LacZ-positive cells and labeling indexes were determined. Transfection was performed in the presence of 10% FBS. Data shown represent mean ±SD. n=3

*4)ND = Not done

*5)Reference: A. Kikuchi et al., *HUMAN GENE THERAPY*, **10**: 947-955 (1999).

7. Transferrin Pre-liposome

Numerous transporters and select markers are expressed on the surfaces of cells; accordingly, with the use of liposomes chemically bound to, for example, transferrin, targeting of cancer cells over-expressing transferrin receptors might become feasible. By using the lipid mixtures available from NOF, it would be possible to prepare liposomes possessing custom cell targeting ability at your own laboratories.

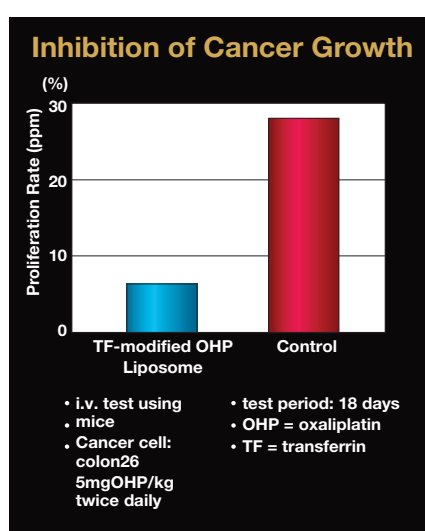
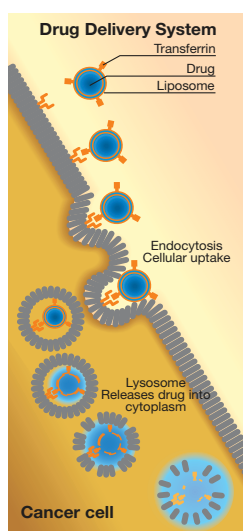
TF-01-PL is a specific lipid mixture containing phospholipids conjugated with phosphatidylcholine and transferrin. If the directions in the instructions provided with your purchase are adopted, drug-containing liposomes with cancer cell targeting ability can be prepared.

癌細胞表面には一般的にトランスフェリンレセプターが多く存在することから、外側表面にトランスフェリンを化学結合させたリポソームを用いることにより、癌細胞へのターゲティングが可能になります。

日油の提供する脂質混合物を使用すれば、癌細胞標的能を有するリポソームをラボにて調製できます。

TF-01-PL は、ホスファチジルコリンやトランスフェリンの結合したリン脂質などを含む特殊な脂質混合体であります。

ご購入の際に添付される方法に従って調製頂ければ、癌細胞標的能を有するリポソームが作製できます。



| Product name | Characteristics |
|--------------|--|
| TF-01-PL | Dried powder consists of PC and other suitable lipids containing transferrin attached phospholipid |

Transferrin-bound liposomes are directed toward the transferrin receptors on the surface of cancer cells.

- Reagent for preparing transferrin-modified liposomes

Preparation of the drug-containing liposomes involves three steps.

- Addition of the drug solution
- Mixing and hydration of the drug with the reagent
- Preparation of the liposomes by size adjustment and sterilization

Increased effectiveness of the drug

- Prolonged half-life of the drug in blood
- Avoidance of RES uptake

Facilitation of R&D of DDS preparations

- Composed of highly purified starting materials, including high-purity phospholipids
- Ready for bulk supply

This product is intended to be used for research purposes only. They are not to be used for drug or diagnostic purpose, nor are intended for human use. They shall not be used as food, cosmetics or utensils, etc.

癌細胞のトランスフェリンレセプターが標的分子

- トランスフェリン結合リポソーム調製試薬

3ステップで薬物内包リポソームを調製

- 薬物溶液の添加
- 薬物と試薬の混合・水和
- 整粒・除菌によるリポソーム作製

薬物の有効性向上

- 長期血中滞留性
- RES 取り込みを回避

DDS 製剤の研究・開発が可能

- 高純度リン脂質をはじめ高純度原料で構成
- バルク供給対応

本製品は、試験研究用試薬としてのみご使用ください。人および動物の医療・臨床診断目的にはご使用しないでください。また、食品、化粧品、家庭用品などとしてもご使用しないで下さい。

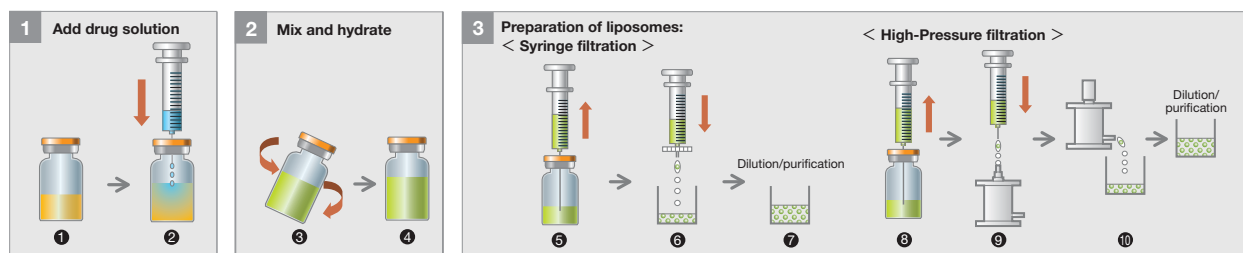
Specifications:

Content: Phospholipid, cholesterol, and transferrin (Human Holo-transferrin)
Volume: Lipid: 20mg, Transferrin: 1mg per vial
Container: 10ml glass vial
Storage: Keep refrigerated

Reference:

- 1) O. Ishida et al., *Pharm. Res.* **18** (7), 1042-1048 (2001)
- 2) H. Inuma et al., *Int. J. Cancer* **99**, 130-137 (2002)

[How to prepare transferrin-modified drug-containing liposomes]



- ① Remove TF-01-PL from the refrigerator and bring to room temperature.
- ② Inject drug solution into the vial.
- ③ Gently shake the vial and mix the drug solution with the TF-01-PL powder to hydrate the powder.
- ④ Shake it gently every 5 minutes for 15 minutes (rolling shakers can also be used) so to ensure the formation of a homogeneous mixture.

Note 1) The amount of drug solution:
This product contains 20 mg lipid in a vial. Addition of the drug solution to obtain a lipid of 1-2% is recommended (the amount of drug solution to be added is 1-2 mL). Be careful not to lose the amount of solution during the filtering process described below, since the amount of solution is very small. Adding 1ml of purified water will make an approximately 30mM phosphate buffer. Adjust the drug solution buffer or salt concentration accordingly.

<Syringe filtration>

- ⑤ Suction the mixed solution prepared in ④.
- ⑥ Attach a disposable cellulose acetate filter (pore diameter: 0.22μm) to the syringe and filter the solution.
- ⑦ Transferrin-modified drug-containing liposomes (particle diameter: approximately 300nm) are obtained.

Note 2) Syringe filtration
This simple method can be employed to prepare liposomes when there are no specific requirements in terms of the liposome diameter or the amount of drug to be encapsulated in the liposomes. Aseptic injection directly into the vial after filtration will provide aseptic filtration at the same time. This product yields approximately 800μl of liposomes when 1ml of the drug solution is used and the solution is filtered with a 13-mm- diameter filter.

<High-Pressure filtration>

- ⑧ Put solution ④ into a pressure filtration system equipped with a polycarbonate filter.
- ⑨ Operate the pressure filtration system to filter the solution.
- ⑩ Transferrin-modified drug-containing liposomes are obtained. The particle diameter will be approximately 200 nm when a 0.2μm pore diameter filter is used. The drug-containing liposomes can be used after dilution or purification as needed.

Note 3) Refining the outer water phase
When the drug-containing liposomes are biologically evaluated, the drug in the outer water phase should be used after purification, according to the purpose of your research. Purification in the outer water phase can be performed by conventional methods, such as ultrafiltration, dialysis, gel filtration and centrifugation.

Note 4) Concentration
Lipid concentration of 10mg/mL (1%) or less is recommended.

Note 5) High-Pressure filtration system
Contact us for further information and purchase.

- ① TF-01-PL を冷蔵庫から取り出し、室温に達するまで放置します。
- ② 薬物溶液を注入します。
- ③ バイアルを振り混ぜ、TF-01-PL 粉末を分散させます。
- ④ 全体を均一にします。
- ⑤ ④をシリンジで吸い上げます。
- ⑥ シリンジに孔径 0.22 μ m のディスポーザブル・セルロースアセテートフィルターを取り付け、フィルターを通します。
- ⑦ トランスフェリン結合-薬物内包リポソームの出来上がり。中心粒径 300nm 程度のリポソームが得られます。

*)本方法は、リポソーム粒径または薬物内包量に特別の要求が無い場合に、簡便にリポソームを調製いただけます。フィルトレーション後、直接無菌的にバイアルに充填すると、除菌ろ過も同時に行うことができます。

- ⑧ ポリカーボネートフィルターを組込んだ加圧ろ過整粒装置に④を入れます。
- ⑨ 加圧ろ過整粒装置を用い、窒素で加圧してフィルターを通します。
- ⑩ トランスフェリン結合-薬物内包リポソームが出来上がります。0.2 μ m のフィルターで整粒した場合は中心粒径 200nm 程度の、0.1 μ m の場合は 150nm 程度のリポソームが一般的に得られます。

加圧ろ過整粒装置は別途お問い合わせ・お求めが必要です。

8. Liposomal Formulations

Optimization & manufacturing of customer's liposome encapsulated hydrophilic, hydrophobic, cationic drugs

Based on our ample experience accumulated in the phospholipid/liposome fields, we are ready to comply with custom manufacture and custom development of the drug-encapsulated liposomes. We can offer proposals for the development of various functional liposomes, such as those with improved half-life of the drug in the blood and those with immunoregulatory functions.

リン脂質・リポソーム分野で培った豊富な蓄積技術に応用し、薬物内包リポソームの受託生産・受託開発を承ります。血中滞留性の向上、免疫調節機能など様々な機能性リポソームのご提案も可能です。

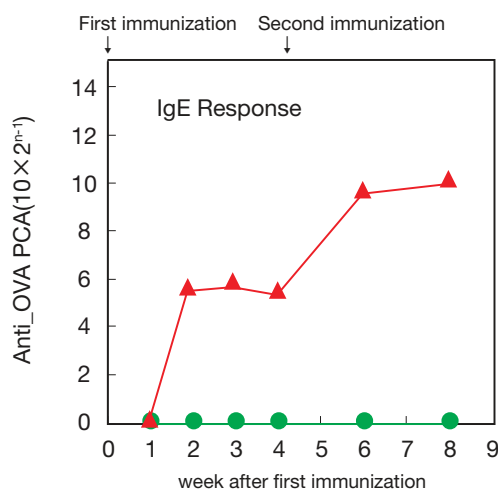
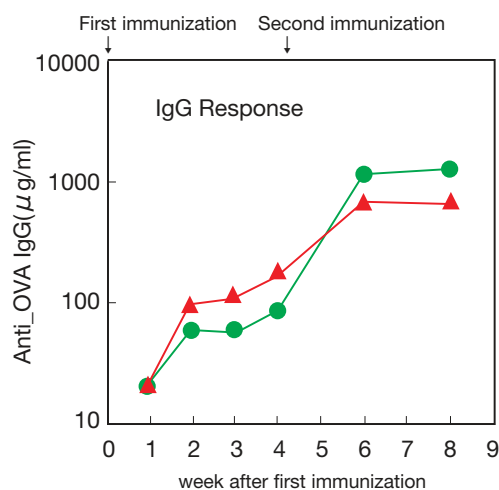
| Functional Liposomes |
|--|
| Long circulation |
| Immuno-regulation (vaccine, allergy-therapy) |

| Characteristics of immuno-regulating Liposomes |
|--|
| NOF has developed immuno-regulating Liposomes |
| Inducing substantial IgG antibody |
| Inducing CTL (Cytotoxic Lymphocyte) |
| Suppressing IgE antibody |



NOF has developed immunoregulatory liposomes and technology. This technology essentially requires production of an appropriate amount of IgG antibody, while concomitantly inhibiting the production of IgE antibody. Due to the well-known advantages of strong cellular immunity (CTL activity), this technology can be applied to the preparation of vaccines for infections and cancer, as well as for the treatment of allergies, including pollen allergy.

免疫系を調節するリポソームを開発しました。この技術は、適量のIgG抗体を産生させつつIgE抗体の産生を抑制するという大きな特長をもってあります。また、細胞性免疫(CTL活性)を強く誘導する特長を有しており、新興感染症、ガンなどのワクチン、花粉症などのアレルギー治療に応用可能な技術です。



▲ Aluminium Adjuvant
● Liposome Adjuvant

Anti-OVA antibody production in mice with immunized Aluminum and Liposomal adjuvants. 8 weeks old female BALBC mice were immunized intraperitoneally. After immunization, blood sample were taken from the tail vein. Anti-OVA antibodies in the sera were determined.

9. LIPONIZER™ for Liposome Production

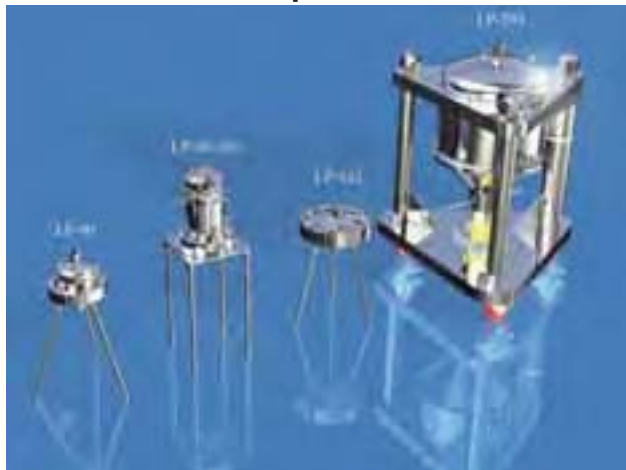
LIPONIZER™ is available only in Japan.

リポナイザーは日本のみの販売となっております。

リボソーム医薬品の製造工程は、脂質原料と API 溶液の水和・分散工程、リボソームの整粒工程からなります。リポナイザーは、リボソームの整粒工程を効率的に実生産スケールで実施するために特別に開発した装置です。メンブランフィルターの穴径を選択することにより、リボソームの粒径を制御することが可能です。

表中のリポナイザーラインナップのほか、API 溶液との水和・分散工程を行うための乳化槽を合わせたパイロットシステムの設計、CIP および SIP などのバリデーションに対応するシステム開発も可能です。

LIPONIZER™ Lineup



| Product name | Filter diameter | Batch size |
|---|-----------------|-------------|
| LIPONIZER LP-90-500 (with 0.5 liter tank) | 90mm | 0.5 liter |
| LIPONIZER LP-90 | 90mm | 3-5 liter |
| LIPONIZER LP-90 + 5 liter tank system | 90mm | 5 liter |
| LIPONIZER LP-142 | 142mm | 5-10 liter |
| LIPONIZER LP-142 + 10 liter tank system | 142mm | 10 liter |
| LIPONIZER LP-293 | 293mm | 25-50 liter |
| LIPONIZER LP-293+ 25 liter tank system | 293mm | 25 liter |

Material: SUS316L , Design pressure : 3MPa

リポナイザー 単体のほか、適切なサイズの加圧用タンクとシステム化が可能です。

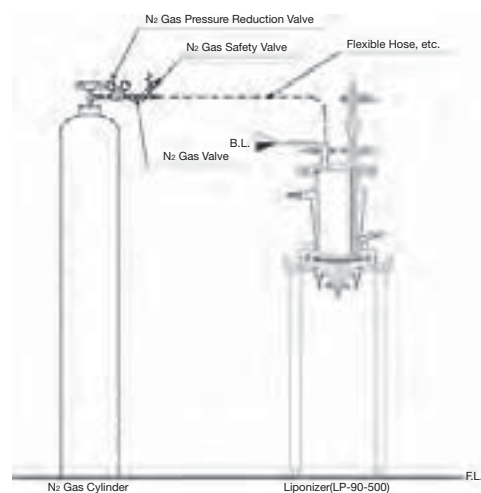
Feed-tank Lineup for LIPONIZER™



LP-90-500 (Cut model)



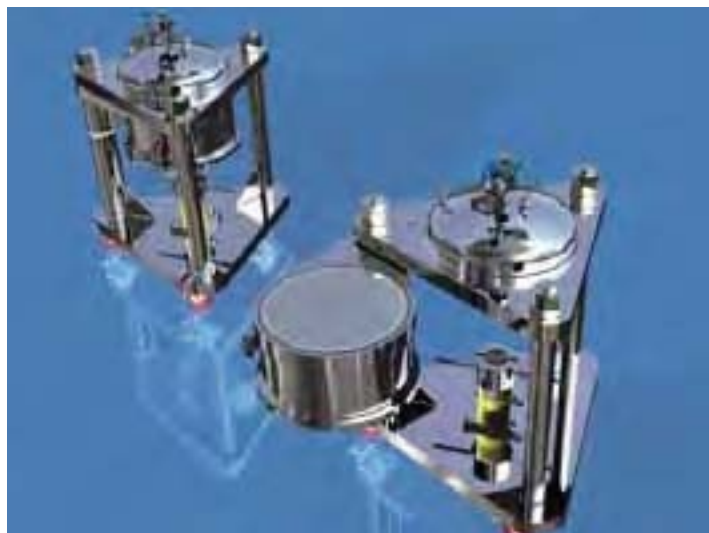
Example of LP-90-500 use



LP-90



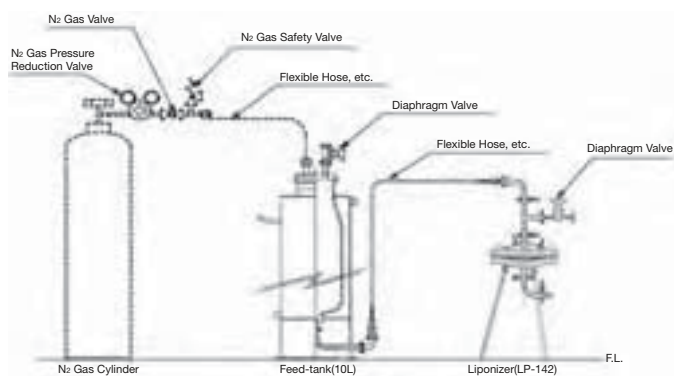
LP-293



LP-142



Example of LP-142 use



10. NOF's Capabilities and Customer Advantages

GMP manufacturing facility

Bulk phospholipids produced at our own validated facility under cGMP operation, have been supplied worldwide commercial drugs for many years, with a good reputation for quality and reliability.



Drug Master Fileings

NOF has already submitted more than 32 DMFs regarding various kinds of NOF phospholipids manufactured to the US FDA, so that customers can rely on our quality. We submit DMFs according to customers' requests and development needs.

Custom Synthesis

Custom synthetic phospholipids and lipids can be produced at customer's request.

Price List for Reagents

Price list for phospholipids is downloaded from the NOF CORPORATION website: <http://www.phospholipid.jp/>. The reagents grades are high quality products as well as GMP products.



Ultra-Purity Polysorbate 80

Polysorbate 80(HX2)TM

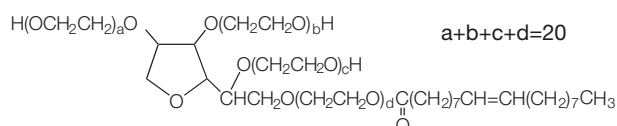
Polyoxyethylene Sorbitan Oleate

Polysorbate 80(HX2) produced by NOF CORPORATION is a high-purity product of the highest quality in the world, with extremely low aldehyde and peroxide levels.

These characteristics contribute to its safety; in a rat study, Polysorbate 80(HX2), as compared to conventional Polysorbate 80 formulations, triggered less histamine release from rat mast cells. The latest in vivo dog study has also indicated less histamine release with our Polysorbate 80(HX2); as a natural consequence, because of the lower incidence of allergy noted, our Polysorbate 80(HX2) has drawn worldwide attention.

日油の高純度オレイン酸誘導体ポリソルベート 80(HX2) は、アルデヒド価や過酸化物価が極端に低い世界最高品質のポリソルベート 80 です。

この特徴は安全性にもつながっており、ラット肥満細胞を用いた試験において、一般のポリソルベート 80 に比較してヒスタミン遊離が少ないという結果が得られています。また、最新のデータでは、犬を用いた In vivo の試験においてもヒスタミン遊離が少ないことが確認されており、アレルギーを起こしにくいポリソルベートとして世界中から注目を集めています。



| Product name | Description |
|---------------------|-------------------------------------|
| Polysorbate 80(HX2) | Polyoxyethylene Sorbitan monooleate |

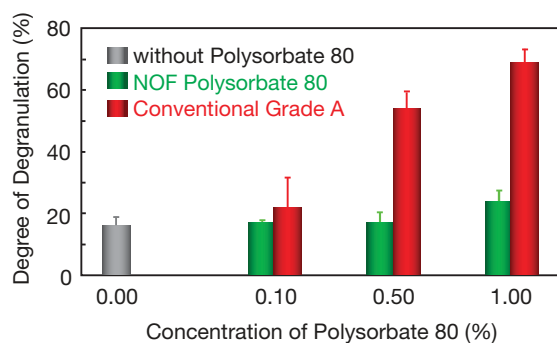
| CAS NO. | Regulatory Status ^{*1} |
|-----------|---------------------------------|
| 9005-65-6 | JP , EP , NF |

^{*1} JP:Japanese Pharmacopoeia
EP:European Pharmacopoeia
NF:National Formulary



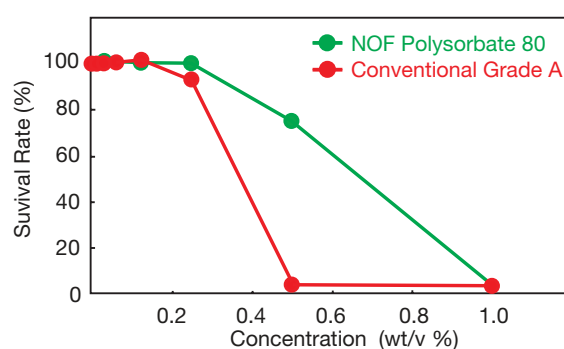
Appearance comparison of Ultra-purity Polysorbate 80

Degranulation Test (An allergic study model)



Effect of Polysorbate 80 on degranulation of RBL-2H3 mast cells. Cells were treated with different concentrations of Polysorbate 80 for 60 mins. The degree of degranulation was determined by measurement of the released β -hexosaminidase into the supernatant.

Cell Toxicity Test



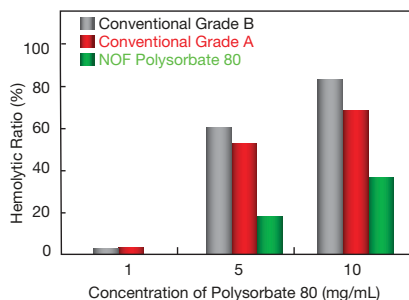
Effect of Polysorbate 80 concentration on the cytotoxicity using SIRC Cells. Cells were treated with each Polysorbate 80 for 24 hrs. The number of viable cells was determined by the Neutral Red Uptake method.

Influence on Basophilic leukocyte



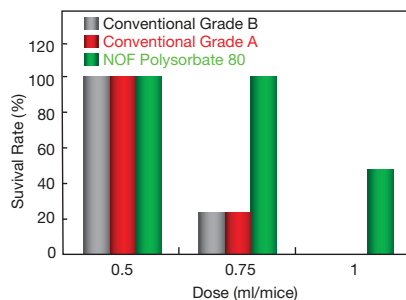
Basophilic leukocytes were immersed in 1% Polysorbate 80 solution for 30 min. The cells were immobilized in glutaraldehyde and observed by SEM.

Hemolysis Test



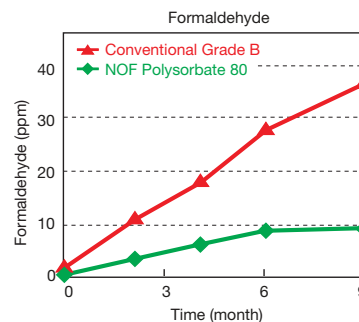
Effect of Polysorbate 80 concentration on the Hemolytic Ratio. Red blood cells from the guinea pig were treated with Polysorbate 80 for 60 mins. The hemolytic ratio was determined by the absorbance of the solution at 576 nm.

Survival Rate



Effect of Polysorbate 80 concentration on the Survival Rate of BALB/c mice. Polysorbate 80 was diluted with PBS and administered to mice by intravenous injection.

Stability Test



This formaldehyde test was performed under N₂ sealed conditions at 40°C.

Status of European Pharmacopoeia (EP)

European Pharmacopoeia (EP) 5th edition stipulates a highest limit for oleic acid (58-85%) in Polysorbate 80. It is paradoxical that the highest-quality Polysorbate 80(HX2) in the world does not satisfy the specification of EP.

As a result of our negotiations with the EP Agency, the upper limit for the content of oleic acid has been eliminated from EP, ed. 5.4.

Now, our Polysorbate 80(HX2) meets the requirements stipulated in the Tripartite Compendia (JP, EP, NF).

European Pharmacopoeia (EP) 5th EDITION に記載されているポリソルベート 80 にはオレイン酸純度の上限が規定 (58 ~ 85%) されており、ポリソルベート 80 (HX2) は EP の規格から外れるという矛盾が生じておりました。

日油が EP 当局に働きかけた結果、EP 追補 5.4 にてオレイン酸純度の上限が撤廃されました。

これにより、日油のポリソルベート 80(HX2) は 3 極 (JP, EP, NF) に対応した製品となります。

IV

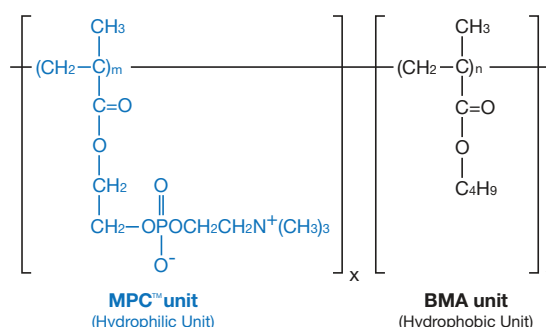
Novel Excipients for Pharmaceutical Development

PUREBRIGHT® MB Series

MPC™ Polymers for Hydrophobic Drug Formulations

NOF provides unique hydrophilic polymers (PUREBRIGHT MB) that allow ready solubilization of hydrophobic drugs in aqueous solutions. These polymers consist of copolymers of 2-methacryloyloxyethyl phosphorylcholine (MPC™) and n-butyl methacrylate (BMA). Introduction of hydrophobic BMA units leads to solubilization of drugs via hydrophobic interactions.

PUREBRIGHT® MB Series は、難溶性の医薬品を水に可溶化させることのできるユニークな水溶性ポリマーです。2-メタクロイルオキシホスホリルコリン (MPC™) と n-ブチルメタクリレート (BMA) とのコポリマーで構成されています。疎水性のBMAユニットを導入することにより疎水結合を介して可溶化されます。



Advantage of PUREBRIGHT® MB Series

- High Solubility Performance for any Hydrophobic Drug
- Phosphorylcholine-Base Biocompatible Polymer
- No Irritation
- No Toxicity
- Nano Particle Drug Delivery possible

High Solubility Performance for any Hydrophobic Drug

1. High Solubility Performance



Lyophilized powder of paclitaxel with PUREBRIGHT MB-37(left) can be easily dissolved in water.

- Paclitaxel : 2mg
- PUREBRIGHT MB-37 : 30mg
- Distilled water : 1mL

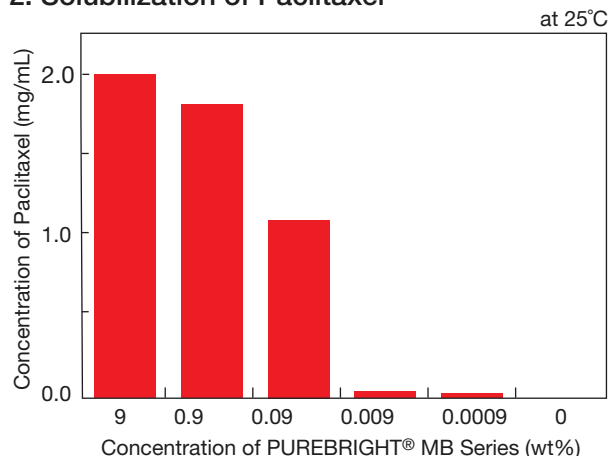
Reference:

T. Konno, J. Watanabe, K. Ishihara, *J.Biomed. Mater. Res.* **65A**, 209-214 (2003)

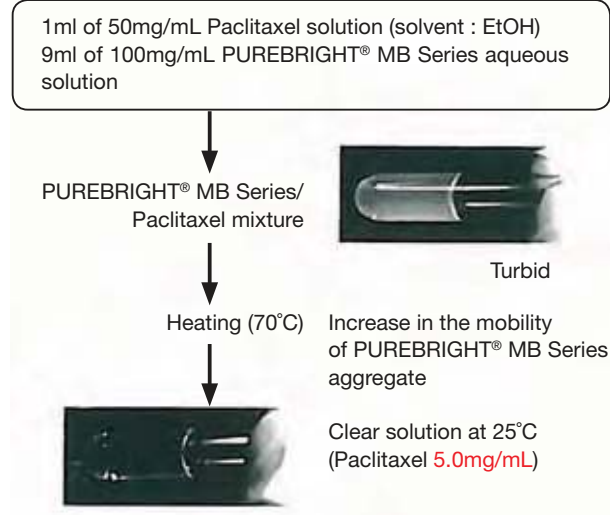
| Product name | Description | MW |
|-----------------------|-------------|------------|
| PUREBRIGHT MB-37-50T | MPC-Polymer | ca.30,000 |
| PUREBRIGHT MB-37-100T | MPC-Polymer | ca.100,000 |

Patent No. : JP3571878, JP4233251, JP4402350, US6214957

2. Solubilization of Paclitaxel



3. Typical solubilization method



4. Relative solubilization activity of PUREBRIGHT® MB series vs. DMSO solution control

| | Abbreviation | Water-solubility |
|---------------|--------------|----------------------|
| AmphotericinB | AmB | 0.0005 mg/mL |
| Camptothecin | CTP | 0.03 mg/mL |
| Paclitaxel | TXL | Less than 0.01 mg/mL |

Reference:

1. T. Konno, et al., *J. Biomed. Mater. Res.* **65A**(2), 209-214 (2003)
2. T. Konno, et al., *Proceed. Int'l. Symp. Control. Rel. Bioact. Mater.* **29**, 464 (2002)
3. M. Wada, et al., *Anticancer Res.* **27**, 1431-1436 (2007)

| Concentration of PUREBRIGHT® MB Series | ratio of abs. from UV | | ratio of peak area from HPLC |
|---|--------------------------|------------|---------------------------------|
| | AmB | CTP | TXL |
| 10 wt% | 100.2 | 5.8 | 735 |
| 1 wt% | 84.9 | 2.8 | 618 |
| 0.1 wt% | 1.8 | 2.8 | 580 |
| 0.01 wt% | 1.4 | 1.4 | 15 |
| 10 wt% DMSO aqueous solution (Control) | 1.0 | 1.0 | 1.0 |

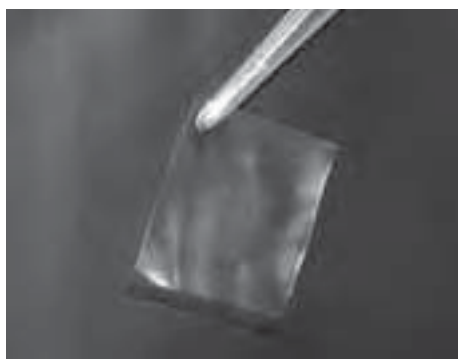
5. Toxicological Data

Safety data of PUREBRIGHT® MB-37 series shows similar activity in comparison with other solubilizers, such as poloxamer and polyoxyethylene castor oil. LDs of more than 25,000mg/kg (mice, orally) and more than 1,000mg/kg (rats, iv) have been obtained.

MB シリーズは一般的な可溶化剤と同等の安全性を有します。
LD₅₀ は 25,000 mg/kg 以上 (マウス経口)、1,000 mg/kg
以上 (ラット経口) のデータが得られています。

| | |
|---------------------------|---|
| Acute toxicity (100T) | Oral LD ₅₀ (Mice) > 25,000 mg/Kg |
| Acute toxicity (50T) | Intravenous injection LD ₅₀ (Rats) > 1,000 mg/Kg |
| Antigenicity (50T) | Negative |
| Mutagenicity (50T) | Negative |
| Skin sensitization (100T) | Non skin sensitization (Guinea pig) |
| Skin toxicity (100T) | Non-primary irritation (Rabbit) |
| Eye irritation (100T) | Practically non-stimulative to eye mucosa (Rabbit) |

6. Unique Feature : Water soluble film of drug and PUREBRIGHT® MB-37 series



Reference:

1. T. Konno, et al., *J. Biomed. Mater. Res.* **65A**(2), 209-214 (2003)
2. T. Konno, et al., *Proceed. Int'l. Symp. Control. Rel. Bioact. Mater.* **29**, 464 (2002)

7. Pharmaceutical applications (published)

1. Oncology Drug Formulation
 - 1) H. Takeuchi et al., *Digestion* **82**, 187-191 (2010)
 - 2) T. Kamei et al., *Cancer Sci.* **102**(1), 200-205 (2010)
 - 3) D. Soma et al., *Cancer Sci.* **100**(10), 1979-1985 (2009)
2. DNA Delivery
 - M. Ukawa et al., *Biomaterials* **31**(24), 6355-6362 (2010)

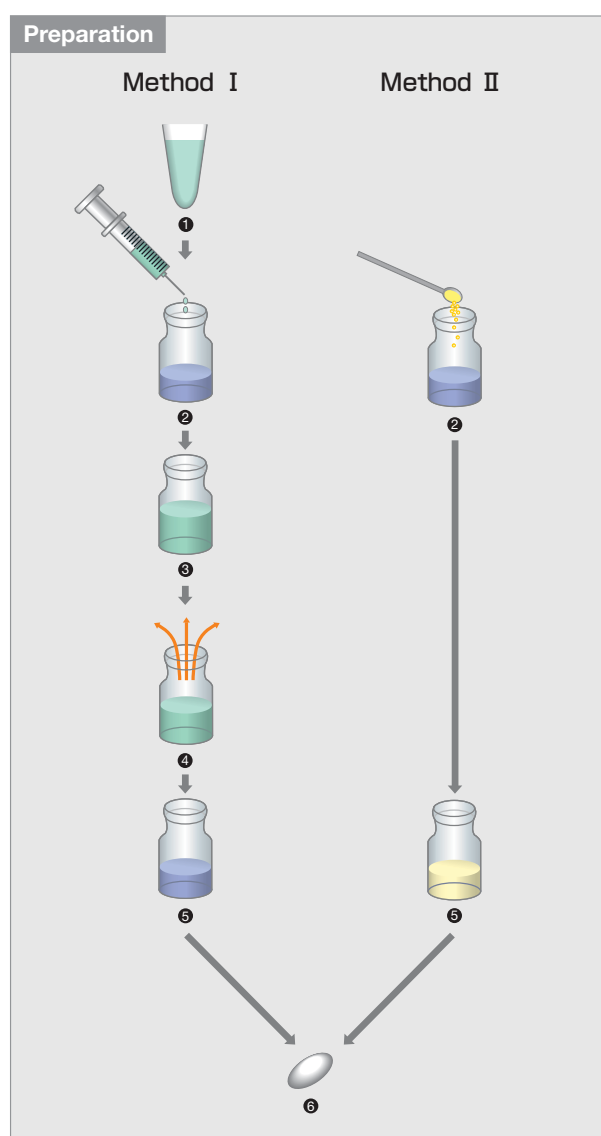
Self-emulsifying Solubilizer SL-11

Novel Nano Formulation for Hydrophobic Drugs

Solubilizer SL-11, occurring as a transparent liquid, can be used to prepare nano-emulsions of various hydrophobic drugs (particle sizes are below 50 nm). Since this possesses excellent self-emulsifying properties, this is the most appropriate agent for SEDDS (Self Emulsifying Drug Delivery Systems). Following oral administration, this solubilizer SL-11 augments intestinal absorption of drugs. Once the hydrophobic drug is dissolved in SL-11 as directed in the attached protocol, SEDDS reagents containing the drug can be easily prepared. NOF has also capability for custom development by using this technology.

Solubilizer SL-11 は透明な液体で、様々な難水溶性薬剤をナノエマルジョン化することができます (粒径 50nm 以下)。また、優れた自己乳化性を有していますので、SEDDS (Self Emulsifying Drug Delivery System) 用基材として最適です。経口投与時に腸管吸収性を増大する効果も認められています。添付のプロトコールに従って難水溶性薬剤を SL-11 に溶解していただくだけで、簡単に薬剤含有 SEDDS 試薬をご調製いただけます。また、この技術を応用した受託開発も承ります。

| Product Name | Content |
|-------------------|--------------------------------------|
| Solubilizer SL-11 | Mixture of pharmaceutical excipients |



Remarks: *Temperature may be changed depending upon drug stability.

[Method I]

- ① Dissolve drug in a suitable solvent, such as ethanol, etc.
薬剤をエタノール等の溶媒に溶解します。
- ② Add the drug solution prepared in ① to Solubilizer SL-11, thoroughly mix to completely dissolve the contents.
Solubilizer SL-11 に①で調製した薬剤溶液を加えて、十分に攪拌し、完全に溶解させます。
- ③ The drug/SL-11 solution with solvent is prepared.
薬剤 / SL-11 溶液
- ④ Evaporate the solvent at 50°C for about 1 hour to remove the solvent, or remove the solvent under a nitrogen stream.
50°C、約 1 時間エバポレートを行い、溶媒を除去します。または、N₂ ガスで溶媒を除去します。
- ⑤ The concentrated solution of SL-11 and the drug is prepared.
薬剤 / SL-11 濃縮液
- ⑥ Soft capsules can be prepared by using the concentrated solution in ⑤.
⑤の濃縮液を用いてソフトカプセル化することもできます。

[Method II]

- ② Depending on the drug, it can be dissolved directly in SL-11. If required, warm the solution to about 50°C to dissolve completely.
薬剤の種類によっては、SL-11 に直接溶解することが出来ます。必要に応じて 50 度程度に加熱し、完全に溶解させます。
- ⑤ The concentrated solution of SL-11 and the drug is made.
薬剤 / SL-11 濃縮液
- ⑥ Soft capsules can be prepared by using the concentrated solution in ⑤.
⑤の濃縮液を用いてソフトカプセル化することもできます。

Cutting-Edge Technology for Self-emulsifying Agents (Particle size: <50nm)

- Easy preparation
- Applicable to various kinds of hydrophobic drugs
- Applicable to soft capsules for oral use
- Most suitable for SEDDS agent
- Improvement of intestinal absorption following oral administration
- Custom development for formulations
- Comply with bulk supply requests

[Specification]

Content : mixture of pharmaceutical excipients
Volume : 50g , 100g , 1kg
Container : glass bottle
Storage : Storage under room temperature.
Keep container closed.

自己乳化型ナノエマルジョン調製試薬 (平均粒径: <50nm)

- 容易に調製可能
- 多様な種類の難水溶性薬剤に適用可能
- 経口用ソフトカプセルに適用可能
- SEDDS 用基材として最適
- 経口投与時の腸管吸収性を向上
- 処方開発の受託
- バルク供給対応

Solubilizer SL-11



8% Probuco in SL-11



Nano Emulsion (0.8% Probuco)

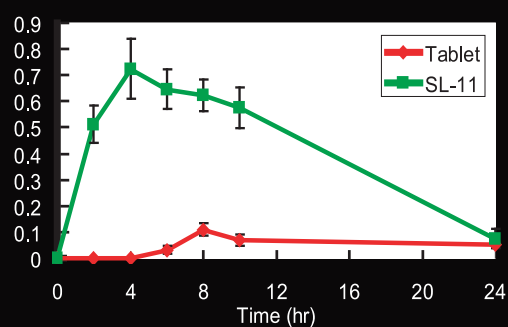


Solubility

| Drug | Pep | IND | NFD | PRB | PTX |
|-------------------------------|-----|-----|-----|-----|------|
| Concentration (%) | 1.0 | 0.5 | 0.3 | 0.8 | 0.25 |
| SL-11 (particle size (nm)) | 22 | 17 | 41 | 26 | 25 |
| POE (35) Castor Oil | I | I | I | I | I |

I : Insoluble

Intestinal Absorption of Probuco



Pep : Peptide type drug IND : Indomethacin
NFD : Nifedipine PRB : Probuco PTX : Paclitaxel

Pharmacokinetics of Probuco

| | SL-11 | Tablet |
|---------------|-------|--------|
| Cmax (g/mL) | 0.724 | 0.109 |
| Tmax (hr) | 4 | 8 |
| AUC (hr*g/mL) | 10.75 | 1.452 |

PUREBRIGHT® SL Series

Hydrophobic Drug Solubilization Kit

NOF produces Solubilization Kits for hydrophobic drugs using our various DDS technologies. The procedures for the use of these kits are very simple, facilitating your screening of new chemical entities at early test stages.

当社はさまざまな DDS 技術を集結し、難水溶性薬剤の可溶化キットを開発しました。キットの使用法は極めて簡単ですので、安全性試験など、新規開発薬剤の初期テストのスクリーニングを容易に行うことができます。



| Product name | Description | Content(Vials) |
|---------------------|-------------------|----------------|
| PUREBRIGHT SL-000-S | PUREBRIGHT SL-110 | 2 |
| | PUREBRIGHT SL-220 | 2 |
| | PUREBRIGHT SL-310 | 2 |
| | PUREBRIGHT SL-350 | 2 |
| | PUREBRIGHT SL-411 | 2 |

PUREBRIGHT®

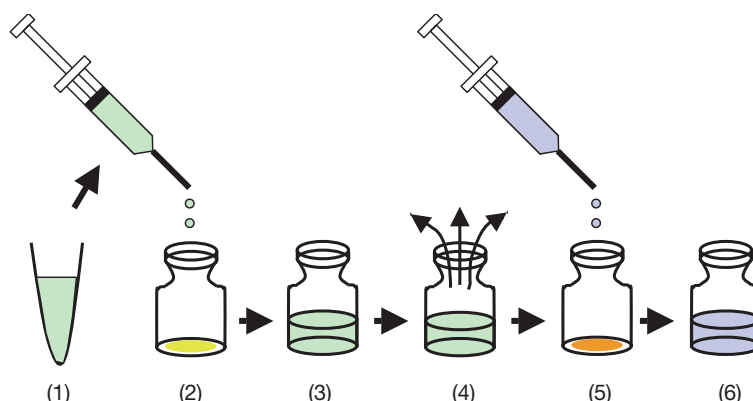
| Product name | Description |
|-------------------------------------|--|
| PUREBRIGHT SL-110 ¹⁾⁻²⁾ | MPC™ polymer based (PUREBRIGHT MB-37-100T) |
| PUREBRIGHT SL-220 | PEG-phospholipid based (SUNBRIGHT DSPE-020CN) |
| PUREBRIGHT SL-310 ³⁾⁻¹⁰⁾ | PEG-cholesterol based1 (SUNBRIGHT CS-010) |
| PUREBRIGHT SL-350 ³⁾⁻¹⁰⁾ | PEG-cholesterol based2 (SUNBRIGHT CS-050) |
| PUREBRIGHT SL-411 | Phospholipid complex based (COATSOME MC-4040/COATSOME MG-4040LS) |

SUNBRIGHT® COATSOME® PUREBRIGHT®

References:

- 1) K. Ishihara et al., *Polym.J.* **31**, 1231-1236 (1999)
- 2) T. Konno et al., *J.Biomed.Mater.Res.* **65A(2)**, 209-214 (2003)
- 3) H. Ishiwata et al., *Chem. Pharm. Bull.* **46**, 1907-1913 (1998)
- 4) Uchegbu IF. et al., *Int. J. Pharm.* **155**, 7-17 (1997)
- 5) Tasset C. et al., *Int. J. Pharm.* **58**, 41-48 (1990)
- 6) Uchegbu IF. et al., *Pharm. Res.* **12**, 1019-1024 (1995)
- 7) Uchegbu IF. et al., *S.T.P. Pharma Sci.* **6**, 33-43 (1996)
- 8) Dimitrijevic D. et al., *J. Pharm. Pharmacol.* **49**, 611-616 (1997)
- 9) Uchegbu IF. et al., *J. Pharm. Pharmacol.* **49**, 606-610 (1997)
- 10) Auth R. et al., *Akt. Dermatol.* **10(6)**, 215-220 (1984)

Hydrophobic Solubilization Methods



< Preparation >

The following instructions are for preparation of 5 vials of the test solution simultaneously.

(1) Weigh drugs into test tube or cuvette according to the desired concentration in the final solution. If you wish to make 1mg/mL of the final solution, weigh 12 mg of the drug, add 3mL of ethanol (select other solvent when drug is not soluble in ethanol) into the test tube, and then dissolve completely by gentle shaking.

(2) Pipette out 500μL of the drug solution, and transfer the solution into each vial of PUREBRIGHT SL Kit respectively.

(3) Dissolve completely by shaking. Warm the vial to 50°C* to obtain a clear solution.

(4) Evaporate the solvent from the vial according to one of the following methods

a) Place the vial into vacuum chamber previously warmed to 50°C*, then evaporate the solvent under vacuum.

b) Evaporate the solvent by a N₂ gas stream at 50°C* over vials placed in a warm bath. Exercise caution in handling to avoid fires or accidents caused by volatile solvent.

(5) Add 2mL of deionized water into the vial, and the dissolve completely with shaking.

Add 1.8mL of deionized water in case of using PUREBRIGHT SL-411.

Drug in aqueous solution (e.g., 1mg/ml) is now ready.

Remarks: *Temperature may be changed depending upon the drug stability.

希望の最終濃度の 4 倍濃度の薬剤 / 溶剤溶液を調製する。

例) 希望最終濃度 1mg/mL の場合、4mg/mL のエタノール溶液を調製する。

PUREBRIGHT SL バイアルに (1) で調製した溶液を 500 μL 加える。

十分に攪拌し、完全に溶解させる。溶解しにくい場合は 50°C 程度まで加温して溶解させる。

エバポレーションにより溶媒を除去する。

例1) 50°C 程度まで加温しながら真空乾燥機でエバポレートする (引火性のある溶媒を用いるときには窒素ガスを流す等して十分に注意してください)。

例2) 50°C 程度まで加温しながら窒素ガス等によりエバポレートする。

イオン交換水を 2mL (PUREBRIGHT SL-411 は 1.8mL) 添加後、十分攪拌を行い、可溶化させる。

1mg/mL の濃度の薬物溶液の完成。

注) 温度は薬剤の熱安定性により調節してください。

Drug Solubilization with PUREBRIGHT® (薬剤の可溶化例)

| Drug | Pep | IND | MPS | CLF | NFD | PRB | CLM | PTX |
|------------------------|-----|-----|------|-----|-----|-----|-----|-----|
| Concentration (mg/mL) | 6.0 | 2.5 | 0.75 | 7.5 | 2.5 | 5.0 | 0.5 | 1.0 |
| PUREBRIGHT SL-110 | I | I | S | I | I | A | I | S |
| PUREBRIGHT SL-220 | S | S | N | I | I | I | I | S |
| PUREBRIGHT SL-310 | S | S | S | S | S | I | S | S |
| PUREBRIGHT SL-350 | I | I | N | N | I | I | I | S |
| PUREBRIGHT SL-411 | S | N | N | N | N | S | N | N |
| Polyoxyl 35 Castor oil | I | I | I | A | I | I | I | I |

PUREBRIGHT & Polyoxyl 35 Castor oil : 3% (w/w) S: Soluble A: Almost soluble I: Insoluble N: No data

Pep: Peptide type Drug

IND: Indomethacin

MPS: Medroxyprogesterone acetate

CLF: Clofibrate

NFD: Nifedipine

PRB: Probucol

CLM: Chlormadinone acetate

PTX: Paclitaxel

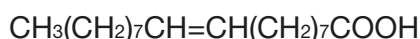
NOFABLE™ Series

Ultra-Purity Oleic Acid and their Derivatives

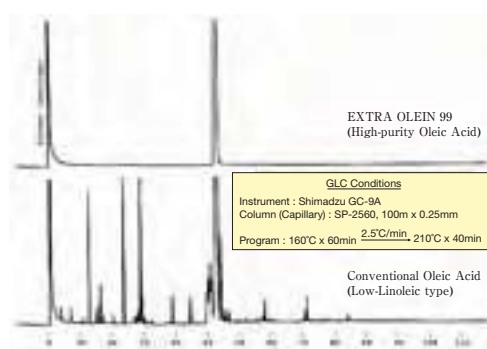
NOF has established the manufacturing processes for 99% oleic acid purity in commercial production scale. Removal of unsaturated fatty acids susceptible to oxidation is eventually associated with improvement of product stability against oxidation, with the result that derivatives with less impurities (peroxides and aldehydes) can be obtained. Ultra-pure oleic acid derivatives are the most suitable for efficacious drug formulations.

99% のオレイン酸を工業的なプロセスで生産する方法を開発しました。酸化され易い不飽和脂肪酸を除去しているので、酸化に対する安定性も向上し、過酸化物質やアルデヒド含量の少ない誘導体が得られ、医薬品用途には最適です。

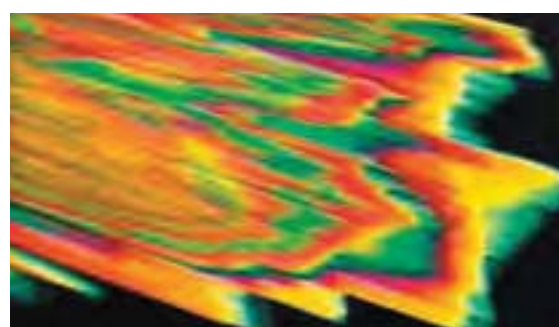
1. Ultra-Purity Oleic Acid <EXTRA OLEIN 99>



| Product name | Description | Oleic acid Content | CAS NO. | Regulatory Status*1 |
|----------------|-------------|--------------------|----------|---------------------|
| EXTRA OLEIN 99 | Oleic Acid | >99% | 112-80-1 | JPE, NF |

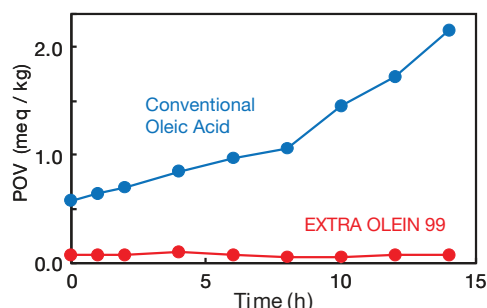


Gas chromatogram for NOF Oleic acid compared to conventional product



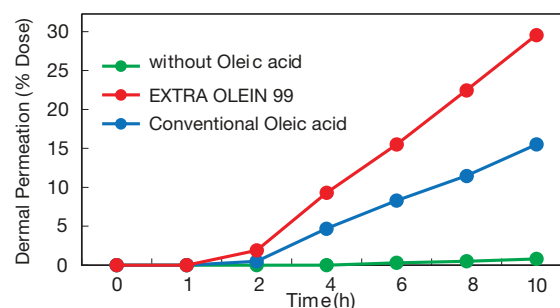
Crystal of EXTRA OLEIN 99

Oxidation Stability of Oleic Acid



Formation of peroxides in oleic acid during incubation at 50°C.

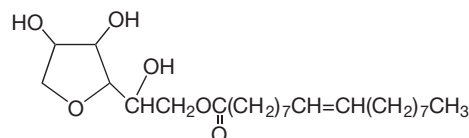
Dermal Absorption Enhancement with Oleic Acid



Dermal Absorption Enhancement of Indomethacin with Highly Purified Oleic Acid (EXTRA Series).

2. Ultra-Purity Oleic Acid Derivatives

•Sorbitan Oleate



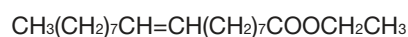
| Product name | Description | Oleic acid Content | CAS NO. | Regulatory Status*1 |
|-----------------|---------------------|--------------------|-----------|---------------------|
| NOFABLE™ SO-991 | Sorbitan monooleate | >99% | 1338-43-8 | JPE |

•Glycerol Oleate



| Product name | Description | Oleic acid Content | CAS NO. | Regulatory Status*1 |
|-----------------|---------------------|--------------------|------------|---------------------|
| NOFABLE™ GO-991 | Glycerol monooleate | >99% | 25496-72-4 | JPE |

•Ethyl Oleate



| Product name | Description | Oleic acid Content | CAS NO. | Regulatory Status*1 |
|----------------|--------------|--------------------|----------|---------------------|
| NOFABLE™ EO-99 | Ethyl oleate | >99% | 111-62-6 | JPE |

*1 JPE : Japanese Pharmaceutical Excipients

SUNBRIGHT® DKH-02HB, DKH-03HB and DKH-04HB

MACROGOL (PEG-200, 300 and 400)

NOF produces top-quality Polyethylene Glycols containing only with extremely low levels of EG (ethylene glycols) and DEG (diethylene glycols), whereby our Polyethylene Glycols can be specifically used as pharmaceutical excipients. From the toxicological perspective, EP has stipulated that the upper limits of EG and DEG should not exceed 4000 ppm, while the USP stipulates that the upper limits of EG and DEG should not exceed 2500 ppm. NOF can guarantee much lower levels of EG and DEG than those stipulated by both EP and USP. In addition, we pride ourselves in the fact that our Polyethylene Glycols contain extremely low levels of impurities, including ethylene oxides, dioxane, peroxides and aldehyde derivatives. NOF can supply high-quality PEG 200, 300 and 400, all of which would meet the specifications of EP, USP, JP and JPE.

Concerning this product, NOF has officially registered its product patent in the United States of America.

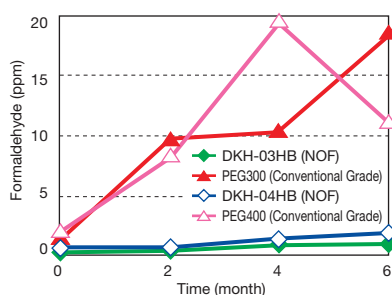
※ Patent No. : US6620976

EG(エチレングリコール)およびDEG(ジエチレングリコール)の極めて少ない医薬品添加剤用ポリエチレングリコールを開発しました。毒性の点からEGとDEGの含有量をEPは4000ppm以下、USPは2500ppm以下に規制しています。当社では、EP、USP規格を大きく下回るEG、DEGの含有量を保証します。さらにエチレンオキサイド、ジオキサン、過酸化物、アルデヒド誘導体などの不純物も非常に低く抑えられています。日油は、高品質かつEP、USP、JPまたはJPEに適合したPEG200、300、400を供給できます。本製品に関しまして、日油の物質特許がアメリカで成立しています。

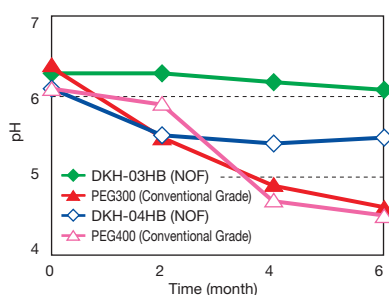
| | Product Name | Description | MW |
|--------|--------------------|--------------------|-----|
| PEG200 | SUNBRIGHT DKH-02HB | Polyethyleneglycol | 200 |
| PEG300 | SUNBRIGHT DKH-03HB | Polyethyleneglycol | 300 |
| PEG400 | SUNBRIGHT DKH-04HB | Polyethyleneglycol | 400 |

SUNBRIGHT®

Stability Test

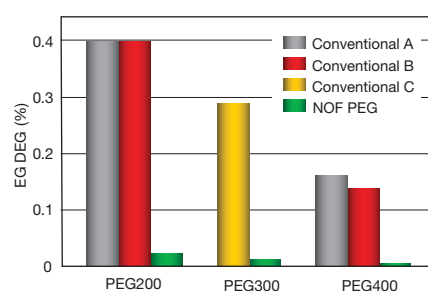


This formaldehyde test was performed under N₂ sealed condition at 40°C.



This pH test was performed under N₂ sealed condition at 40°C.

EG/DEG Content



Specifications

| ITEM | Method | Specification | | |
|--|--------|--|----------|----------|
| | | DKH-02HB | DKH-03HB | DKH-04HB |
| Completeness and color solution | | Pass | | |
| Viscosity | | 3.9-4.8 | 5.4-6.4 | 6.8-8.0 |
| Average molecular weight | | 190-210 | 285-315 | 380-420 |
| pH | | 4.5-7.5 | | |
| Residue on ignition (%) | USP | NMT 0.1 | | |
| Heavy metals (ppm) | | NMT 5 | | |
| Free ethylene oxide and 1,4-dioxane (ppm) | | NMT 10 (Ethylene oxide : NMT 1, 1,4-Dioxane : NMT 10) | | |
| Limit of ethylene glycol and diethylene glycol (%) | | NMT 0.05 | | |
| Organic volatile impurities | | Pass | | |
| Peroxide value (meq/Kg) | NOF | NMT 3 | | |
| Formaldehyde (ppm) | | NMT 5 | | |

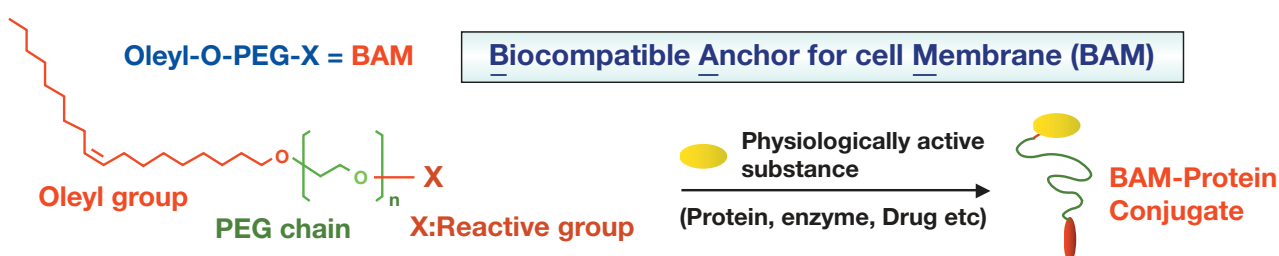
NOF can also supply products without anti-oxidant agent, BHT.

SUNBRIGHT® OE Series

Biocompatible PEG Anchors for Cell Membrane Insertion [BAM]

NOF supplies a unique Biocompatible Anchor for cell Membranes (BAM), without eliciting observable cell damage. BAM contains both oleyl groups as a hydrophobic cell membrane anchor and polyethylene glycol (PEG), which imparts hydrophilicity. Its chemical structure is designed to have various reactive groups at the PEG terminals allowing them to attach to physiologically active substances or surfaces of materials. Employment of BAM enables researchers to modify the surfaces of cells and tissues with physiologically active substances, such as proteins or drugs without injuring cells and tissues, and also to immobilize live cells and tissues on the surfaces of various kinds of materials. Since BAM exerts excellent cell interfacing functions beyond conventional concepts, it can be extensively used in pharmaceuticals and cosmetics.

細胞にダメージを与えない細胞膜修飾剤 (BAM : Biocompatible Anchor for cell Membrane) を開発しました。BAM は細胞膜へのアンカーとして脂質オレイル基と、水溶性を高めるためのポリエチレングリコール (PEG) からなり、生理活性物質や材料表面に結合させるため PEG 鎖末端に各種の反応性基を導入した構造を有します。BAM を用いることにより、細胞や組織にダメージを与えることなく、細胞や組織の表面を蛋白質や薬剤などの生理活性物質で修飾することや、細胞や組織を生きたまま各種材料表面に固定化することが可能となりました。従来のコンセプトを超えた機能を持っており、医薬品、化粧品分野で広い用途が期待されます。

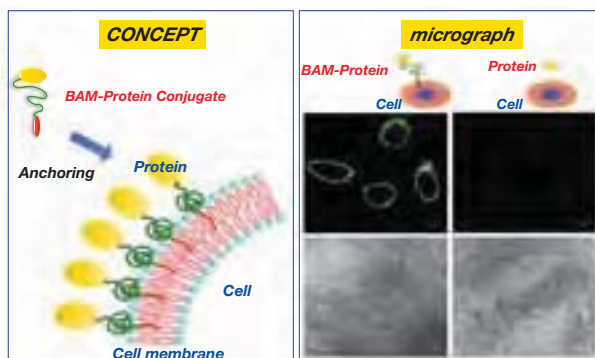


| Product name | Reactive Group (X) | Mw |
|--------------------|--|-------|
| SUNBRIGHT OE-020CS | | 2,000 |
| SUNBRIGHT OE-040CS | -CO-CH ₂ CH ₂ -COO-NHS | 4,000 |
| SUNBRIGHT OE-080CS | | 8,000 |

SUNBRIGHT®

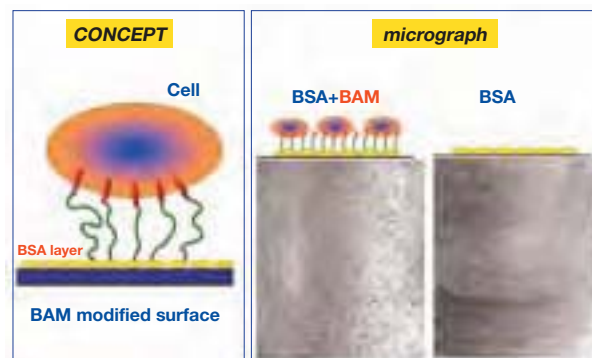
Application I :

Anchoring of BAM-Protein conjugate to the cell membrane



Application II :

Anchoring of cell on a BAM modified surface



References:

- 1) K. Kato, et. al, *Biotechnol. Prog.* **20**, 897-904 (2004)
- 2) K. Kato, et. al, *BioTechniques* **35**,1014-1021 (2003)

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| | |
|---|--|
| In the Americas <u>NOF AMERICA CORPORATION</u> One North Broadway, Suite 1012 White Plains, NY 10601, USA Tel : 914-681-9790 Fax : 914-681-9791 E-mail : info@nofamerica.com Home Page : http://www.nofamerica.com | In the region except in Americas, Europe <u>NOF CORPORATION</u> DDS Development Division 20-3 Ebisu 4-chome, Shibuya-ku Tokyo, 150-6019, Japan Tel : +81 3 5424 6741 Fax : +81 3 5468 0901 E -mail : ddsinfo@nof.co.jp Home Page : http://www.dds-drug.com |
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| A faxed confirmation is required for every order | |

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価格：買主は、請求書に記載されている銀行口座へ電信送金することにより支払うものとします。注文の前に買主が価格情報を必要とする場合、買主は売主に見積価格を問い合わせるものとします。見積価格は、発行後30日間有効です。注文の際、買主は売主の見積価格または見積番号に言及する必要があります。売主は、買主の注文に対して価格やその他の条件に相違がある場合、電話、ファックスまたは電子メールで買主に連絡するものとします。

保証：売主は、買主に対し、購入された製品の試験成績書を発行します。買主は、上記の「検査」の項目で示されている5日以内（製品の不足、明らかな欠陥または損傷があった場合）または当該製品の請求書記載の日付から30日以内（その他製品に欠陥があった場合）に、当該不足等につき書面で売主に通知し、それを受けた売主は、製品到着日付から30日以内に、売主の判断によって、材料または製造上に欠陥のあるすべての製品を再処理または交換いたします。

上記は買主の唯一の救済手段です。売主は明示、黙示を問わず、上記以外の商品性、特定目的への適合性など（を含むがこれに限られない）、他のすべての保証および責任を明示的に放棄するものとし、買主は自らを選択する特定の使用から生じるすべてのリスクを負います。買主は売主の要望に応じて残金を支払うものとします。支払いの遅延においては、買主はすべての費用（買主の不履行から生じる合理的な弁護士、会計処理手数料および他の集金費等を含みますが、これに限られません）を支払うものとします。支払いが完結するまで年間あたり6%の遅延損害金が生じるものとします。

売主の唯一の責任である、買主の唯一の法的救済とは、買主が売主の指示に従って製品を返還した後、売主の判断により、費用をかけず、また購入代金の返金をせずに、製品を交換もしくは再処理するものとします。

売主の重大な過失により生じた場合を除き、売主は、買主から当該損害等（利用機会の損失、仕掛品の損失、故障時間、収入・収益の損失、節約の失敗、買主の製品の損失、その他当該損害等に基づく買主の第三者に対する責任または当該製品によって生じた労働力もしくはその他の費用を含むがこれに限られない）の可能性について説明を受けていた場合であっても、一切の間接的、偶発的、刑法上または特別の損害について責任を負いません。当該損害が、契約不履行、保証、不法行為（過失を含む）、無過失責任（厳格責任）その他により生じたものであるか、それらによる結果であるか否かを問いません。買主または第三者の行為または不作為により生じる、あるいはそれらにより生じたいかなる損失、請求、費用、または損害に対しても責任を負いません。契約または不法行為によるものであるかを問わず、賠償責任総額は購入金額を超えないものとします。すべてのクレームは、その性質如何にかかわらず、出荷後1年以内に提起されなければなりません。

法令遵守：売主は、製品を日本の労働基準法（改正された場合には改正後の法律）、これに関する規制、規則、命令の規定に可能な限り準拠して生産することを約束します。

買主の表明および補償：買主は下記の「買主による製品の使用」のとおり、購入したすべての製品を使用することおよび当該使用がいかなる法や規則にも違反しないことを表明および保証します。買主は、売主に対し、直接的または間接的であるかを問わず、製品の使用または製品の債務不履行により生じた、買主（役員、代理人、従業員、承継人や譲受人を含む）、買主の顧客、エンドユーザー、補助職員（貨物操作者など）または第三者により提起された、過失、保証違反、不法行為上の厳格責任、契約その他あらゆる法律上の理論によって生じる売主、売主の従業員、代理人、承継人、役員および譲受人に対する訴訟、損失、請求、要求、責任、費用及び経費（弁護士および会計上の費用を含む）を補償するものとします。買主は売主に対して、製品が関与して起きた人身事故や物損事故等のすべての事故や事件の情報につき、認知してから15日以内に書面で通知するものとし、買主は売主に対して、調査および事故の原因究明に全面的に協力するものとし、買主により作成され、または買主が第三者から提供された、全ての書面、報告および試験結果を提供するものとします。買主の売主に対する上記の情報または事故報告の情報の提供は、いかなる場合であっても当該事故または事件に関する責任の承継を意味することはありません。

守秘義務：買主は、「販売」に関して売主から印字その他の方法で「秘密」であることを明示され、または「秘密」であると告知されて開示されたデータ（電子データを含む）、文書または「製品」に関するサンプル（以下「本秘密情報」と総称します。）を売主の事前の書面による承諾を得ることなく、第三者に対して開示または漏洩してはならず、かつ、この「販売に関する条件」以外の目的に使用してはならないものとします。

上記の規定にかかわらず、次の各号のいずれかに該当することを書面その他、客観性のある証拠により証明できる情報は、本秘密情報から除外されるものとします。

- (1) 開示を受けた際、既に公知または公用であった情報
- (2) 開示を受けた後、買主の責めに帰することができない事由によって公知または公用となった情報
- (3) 開示を受けた際、既に買主が保有していた情報
- (4) 正当な権限を有する第三者から秘密保持義務を負うことなく買主が適法に開示を受けた情報
- (5) 開示を受けた秘密情報によることなく買主が独自に開発した情報

買主は、適用法令、規制、裁判所の命令に従うため、または臨床実験を行い買主の製品を商業的に販売するのに必要な許可を得るために本秘密情報の開示を要求された場合は、以下の各号の措置を講ずることに条件に、当該命令または要求の目的に限り、当該本秘密情報を開示することができるものとします。

- (1) 開示先および開示する内容について、売主の事前の承諾を得ること
- (2) 命令、または要求された部分に限り開示すること
- (3) 開示に際して、当該本秘密情報が秘密である旨を開示先に対し、書面により明らかにすること

技術サービス：買主の要望に応じて、また売主の独自の判断により、売主は買主に対して製品に関する技術サービスを提供します。売主は、明示または黙示を問わず、技術サービスまたは両当事者の従業員によって提供された情報に関して、商品性、特定目的への適合性を含む、いかなる保証もしません。売主による本製品の使用、選択、応用または適合性に関する示唆（提案）は、売主の役員または代表権を有する代表者が署名した文書による相互の合意がある場合を除き、一切保証と解釈されることはありません。

買主による製品の使用：買主は、売主の製品が主に研究を目的として開発されたものであり、製品ラベル、売主の製品カタログ、または買主に対する説明書などに特に記載がない場合は、対外診断薬用を使用することや、商業目的で人体および動物への食品、医薬品、医薬材料、化粧品などに使用することを含み、他の目的には使用しないことを同意または認識するものとし、売主は、買主に提供された説明書に記載がない限り、本製品の食品、医薬品、医療材料、化粧品または商業用途、他目的への安全性および効能の試験をしておりません。

侵害：買主は、製品に関連し、いかなる国における特許、実用新案、意匠、商標、著作権、営業秘密その他の知的財産権を含むがそれに限らない侵害（以下「侵害」という。）について、売主を免責し、害の及ばないようにするものとする。売主は、自らの費用において、侵害に関する請求、訴訟、訴訟手続きに対して弁護士、解決し、または対処するものとする。

返品：製品は売主の許可がない限り返品することができます。返品の際には売主の返品の際の輸送に関する指示に厳格に従うものとする。

雜則：買主の債務不履行に対する売主の権利放棄または売主による本販売条件の履行および本販売条件に基づく権利義務の不行使は、(a) 将来発生しうる、または (b) 以後の売主の本販売条件を実施する権利を放棄したものとみなしません。販売における権利および救済は全てコンモノー上又はエクイティ上、売主が持つその他の権利と重複するものとします。本販売条件中の条項の一部が何らかの法に抵触するかまたは同法上無効とされる場合であっても、本販売条件のそのほかの条項の妥当性、適法性および法的強制力に対しては影響を及ぼさないものとします。段落の見出しはここに便宜上のものであり、本販売条件の構成部分ではなく、その解釈に影響を及ぼすものではありません。本販売条件は、各当事者とその承継人、法定代理人および権利譲受人の利益に帰し、これらの者に対して拘束力を有するものとします。

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